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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

VICTOR MENASHE, Individually and On Behalf of All Others Similarly Situated, Plaintiff, v. BIOGEN INC., MICHEL VOUNATSOS, JEFFREY D. CAPELLO, and MICHAEL R. MCDONNELL Defendants.	**CASE No.: 1:21-cv-10479-IT** **AMENDED CLASS ACTION COMPLAINT FOR VIOLATION OF THE FEDERAL SECURITIES LAWS**

Lead Plaintiff Nadia Shash and Named Plaintiff Amjad Khan, individually and on behalf of all other persons similarly situated, by their undersigned attorneys, for their complaint against Defendants (defined below), allege the following based upon personal knowledge as to themselves and their own acts, and information and belief as to all other matters.

I. INTRODUCTION[1]

1. This is a federal securities class action on behalf of all persons or entities who purchased or otherwise acquired publicly traded Biogen securities between October 22, 2019 and November 6, 2020, inclusive ("Class Period"). Plaintiff seeks to recover compensable damages caused by Defendants' violations of the federal securities laws under the Securities Exchange Act of 1934 ("Exchange Act.") [2]

2. Shortly after Biogen announced it was terminating its two Phase III clinical trials for its potential blockbuster Alzheimer's treatment, aducanumab, because a pre-planned futility analysis showed it was highly unlikely the trials would meet their clinical endpoints, in its efforts to revive the prospects of United States Food & Drug Administration ("FDA") approval, Defendants manipulated the clinical data and recklessly lied to investors about the results of those studies. Defendants omitted from their disclosures historical data they were duty-bound to disclose and instead, spun a positive conclusion that they contrived from the data they improperly withheld, defying the actual results of the clinical trials and violating the norms of statistical analysis.

[1] Unless otherwise noted, all emphases are added.

[2] Excluded from the class are defendants, all officers and directors of Biogen, their immediate family members and any entity over which an excluded person exercises control or owns more than 10%.

3. During the Class Period, Defendants consistently repeated their false narrative that that the only reason the studies had failed to show efficacy is because patients had not received a sufficient number of high doses of aducanumab. Based on additional data collected since the futility determination and on a sub-group analysis, Defendants claimed the trials showed that aducanumab was effective in patients that received a sufficient number of high doses. Defendants also misrepresented that there was a strong correlation between reduction of amyloid plaque biomarkers and positive clinical outcomes, which, were it true, would validate Biogen's mechanism of action: slowing cognitive decline by reducing amyloid plaque. At the same time, Defendants concealed a host of statistical analyses of the trial data for Studies 301 and 302 that showed that aducanumab provided no clinical benefit regardless of the number of doses, and that there was no correlation between reduction of amyloid plaque and positive clinical outcomes.

4. Based on these fraudulent analyses, Biogen sought approval for aducanumab, filing a biological licensing application ("BLA"). The FDA scheduled a meeting of its Peripheral and Central Nervous System Drugs Advisory Committee ("Advisory Committee"), publishing a briefing book several days before the meeting. In the briefing book, the FDA, by its Office of Neuroscience, included its opinion that aducanumab effectively treated Alzheimer's disease. At the Advisory Committee meeting, however, the ten-member panel excoriated Biogen for its presentation, found "no persuasive evidence to support approval of aducanumab at this time," and voted 10-0 against approval. The Advisory Committee based its decision in large part on the correct statistical analyses that Defendants had concealed from investors. The NASDAQ market halted trading on Biogen's stock on the day of the Advisory Committee meeting. When trading resumed on November 9, 2020, the price of Biogen's stock plummeted 28.2%, from its previous close of $328.90 to close at $236.26.

Summary of the Case

5. Defendants staked Biogen's future on an Alzheimer's treatment, aducanumab. Aducanumab removes amyloid plaque, which is present in the brains of Alzheimer's patients. Removing plaque, Biogen hopes, slows down the progression of Alzheimer's disease. If it obtained FDA approval, aducanumab would become the first disease modifying therapy for a disease that afflicts millions of Americans.

6. Aducanumab's Phase III clinical trials consisted of two identically designed international studies, Study 301 (also known as ENGAGE) and Study 302 (EMERGE), each with about 1,600 patients. Each study was divided into three arms of equal size: placebo, low dose and high dose. The studies' primary endpoint was the change in CDR-SB scores, a measure of cognitive and functional decline, after 18 months. Aducanumab was not expected to improve (lower) CDR-SB scores, or even maintain cognitive abilities, but only to slow cognitive and functional decline.

7. In March 2019, Biogen halted aducanumab's clinical trials because, based on a pre-specified intermediate "futility" analysis, aducanumab had failed to show efficacy and it was highly unlikely the clinical trials would reach their endpoints if continued to conclusion. Defendants had lost their bet.

8. Biogen's stock price collapsed. It faced a bleak future. Its sales were declining, and its patents were either expiring or under legal challenge. Defendants' personal futures looked bleak, too: shepherding Biogen through its slow decline to extinction is hardly an executive's dream job.

9. With no plausible replacement, Defendants sought to resuscitate aducanumab.

10. Using additional data collected between when the futility database was locked and when futility was declared, Biogen was able to find one of the studies – Study 302 – just barely statistically significant on its endpoints.

11. But Defendants needed something more. Study 301 was a negative study. In fact, in Study 301, patients on high dose aducanumab did worse than placebo. When the FDA receives an application with one positive and one negative clinical study, it will – at best – ask the sponsor to run another confirmatory trial. Because the measure of aducanumab's effectiveness is whether it produces results after 18 months and recruiting a sufficient number of patients takes time, another trial would take 3 years or more.

12. Defendants wanted to avoid that fate. So they tasked 49 of Biogen's statisticians, under close supervision from the head of Biogen's Alzheimer's Disease program Defendant Samantha Budd Haeberlein and Chief Medical Officer Defendant Alfred Sandrock, with sifting through Study 301 data to find anything that might support aducanumab's approval.

13. Defendants announced aducanumab's revival on an October 2019 conference call that begins the Class Period. Defendants told investors, both then and when they presented more data in December 2019, that their analysis showed Study 301 supported, or at least did not undermine, Study 302.

14. Defendants had amended the trials' protocol in March 2017. The amendment altered the maximum possible dose for patients who carried a gene that predisposed them to Alzheimer's Disease (ApoE ε4, or APOE4 herein), who made up two thirds of the study population. Before the amendment, these patients received only 6mg/kg for the high dose because

their genes also predispose them to an aducanumab side effect, ARIA.[3] After the amendment, they received the full 10mg/kg high dose.

15. Defendants claimed that giving patients anything less than 10mg/kg was ineffective. They told investors that Study 302 was positive – and Study 301 negative – because fewer APOE4 carriers in Study 301 received the maximum dose. More, they said, aducanumab had worked precisely as it was intended to. It had removed plaque, a biomarker, and the removal of plaque directly correlated with better clinical outcomes for the patients. Here, they paused to note, less plaque had been removed from patients in Study 301 than in Study 302 – which explains why Study 301 was a negative study.

16. Defendants' statement that removal of plaque correlated with – and even caused – better clinical outcomes was outright false. There was no correlation. In fact, in Study 302, plaque removal was associated with *worse* clinical outcomes.

17. Defendants' statements that patients who received more 10mg/kg doses saw better clinical outcomes were highly misleading. In Study 302, patients who received 6mg/kg performed just as well – slightly better, in fact – than patients who received 10mg/kg. The number of 10mg/kg doses, which Defendants said was critical in Study 301, had no impact in Study 302. And APOE4 non-carriers, who should have received the greatest benefit of all because they always received the 10mg/kg dose and their treatment was never interrupted by side effects, saw no benefit at all in both Study 301 and 302.

[3] ARIA is an acronym for Amyloid Related Imaging Abnormalities thought to represent vasogenic edema and cerebral micro-hemorrhages. ARIA were first reported in 2009 in clinical trials of bapineuzumab1,2 and have since been associated with other investigational anti-Amyloid Beta monoclonal antibodies for the treatment of Alzheimer's disease.

18. Yet Defendants concealed the data that would have shown their explanations were false. They concealed data on the correlation between biomarkers and clinical results, as well as data for the subgroups consisting of patients who were and were not genetically predisposed to Alzheimer's Disease.

19. Thus, the true story Defendants' statements concealed, was that a certain sub-group of patients in Study 301 had performed better than others, not because aducanumab had any different effect, but because it will always be the case that through random chance certain patients will show better test results than others. When Biogen's 49 statisticians carefully searched the study data for months they were bound to identify a sub-group that had an adequate response to the test drug. Because they withheld the data that proved them wrong, Defendants' false narrative convinced investors and even world-renowned Alzheimer's Disease specialists that Study 301 was at least explicable, and that at best it supported Study 302 by showing that aducanumab was effective at the 10mg/kg dose.

20. On November 6, 2020, aducanumab appeared before an FDA advisory committee ("Advisory Committee"), a group of experts who hold a public hearing to discuss the merits of product applications and advise the FDA on specific questions it poses. The briefing materials for the meeting included, but buried, a report by Tristan Massie, PhD, the statistical reviewer for the aducanumab file. To draft his report, Dr. Massie had access to the raw data denied the public and researchers. He was able to run the analyses Biogen had concealed from investors. And his report showed that Defendants' statements had been false; that there was no correlation between removal of amyloid plaque and clinical outcomes; that though Defendants said there were too many patients on the 6mg/kg dose for Study 301 to be effective, in truth there was no difference between patients who received 6mg/kg or 10mg/kg in Study 302; and that a full one-third of patients who

always received the full number of 10mg/kg doses, the APOE4 non-carriers, saw no benefit in either Study 301 or 302.

21. The advisory committee voted 10-0 against approving aducanumab. Their decision was based principally on the analyses Dr. Massie ran in his report showing that aducanumab provided no clinical benefit to Alzheimer's patients.

22. Approving an ineffective Alzheimer's drug would be a public policy disaster. Beyond the waste of tens of billions of dollars a year for an ineffective drug, running PET scans to diagnose patients and running routine MRI scans to monitor for side-effects would strain the Nation's healthcare system. Recruiting for trials for new Alzheimer's treatments that might actually be effective would become challenging, as patients would want to take aducanumab which, though ineffective, bears the FDA's stamp of approval. Patients would spend some of their few remaining lucid years at their doctors' offices being injected with a drug that doesn't work. Some would develop serious and perhaps lethal side effects. As an aducanumab site investigator and standing (though recused) member of the advisory committee explained in a letter urging the committee to vote against aducanumab, "the evidence shows it will offer improvement to none, it will harm some of those exposed, and it will consume enormous resources."

23. Biogen's stock was halted all day on November 6 because of the Advisory Committee meeting. When it resumed trading on November 9, the price of Biogen's stock fell from its previous close of $328.90 to fall to $236.26, down 28.2%.

II. JURISDICTION AND VENUE

24. The claims asserted herein arise under §§10(b) and 20(a) of the Exchange Act (15 U.S.C. §§78j(b) and §78t(a)) and Rule 10b-5 promulgated thereunder (17 C.F.R. §240.10b-5).

25. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §1331 and §27 of the Exchange Act.

26. Venue is proper in this judicial district pursuant to §27 of the Exchange Act (15 U.S.C. §78aa) and 28 U.S.C. §1391(b) as the alleged misstatements entered and the subsequent damages took place in this judicial district.

27. In connection with the acts, conduct and other wrongs alleged in this Complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including but not limited to, the United States mail, interstate telephone communications and the facilities of the national securities exchange.

III. PARTIES

28. Lead Plaintiff Nadia Shash, as set forth in her PSLRA Certification which was previously filed and is incorporated by reference, purchased Biogen securities at artificially inflated prices during the Class Period and was damaged thereby.

29. Named Plaintiff Amjad Khan, as set forth in his PSLRA Certification which is attached as an exhibit hereto and incorporated by reference, purchased Biogen securities at artificially inflated prices during the Class Period and was damaged thereby.

30. Defendant Biogen Inc. is a Delaware company headquartered in Cambridge, Massachusetts. Biogen discovers, develops, and manufactures products to treat neurological and neurodegenerative diseases, as well as autoimmune and hematologic disorders. Biogen's principal product is aducanumab, an investigational biologic studied for the treatment of Alzheimer's disease. Biogen's securities trade on the NASDAQ Exchange under the ticker symbol "BIIB".

31. Defendant Michel Vounatsos has served as the Company's CEO and as a Director since January 2017.

32. Defendant Alfred W. Sandrock, Jr., has served as Biogen's Chief Medical Officer since October 2015. He served as Executive Vice President – Neurology Discovery and Development from October 2015 to October 2019, when he was promoted to the position of Executive Vice President – Research & Development.

33. Defendant Samantha Budd Haeberlein served as Biogen's Vice President of Clinical Development from February 2015 through March 2020, and has served since then as its Senior Vice President – Head of Neurodegeneration Development Unit.

34. Defendants Vounatsos, Sandrock, and Budd Haeberlein are the "Individual Defendants."

35. The Company is liable for the acts of the Individual Defendants and its employees under the doctrine of *respondeat superior* and common law principles of agency because all of the wrongful acts complained of herein were carried out within the scope of their employment.

36. The scienter of the Individual Defendants and other employees and agents of the Company is similarly imputed to the Company under *respondeat superior* and agency principles.

37. The Company and the Individual Defendants are referred to herein, collectively, as the "Defendants."

IV. BACKGROUND

A. The Amyloid Hypothesis

38. In patients suffering from Alzheimer's disease, brain cells that process, store and retrieve information degenerate and die. Yet while Alzheimer's progression is reasonably well understood, its causes remain unclear.

39. First proposed in 1991, the amyloid hypothesis attributes the disease to build-up of a protein called amyloid-beta (also known as Aβ).

40. Amyloid-beta is a fragment of a larger protein, amyloid precursor protein, commonly known as APP. APP is produced in large quantities in neurons. When it functions normally, it is quickly cleaved into various proteins and metabolized.

41. One form of cleavage results in the production of single amyloid-beta molecules (monomers). Single amyloid-beta molecules are easily metabolized because they are water soluble. But in some circumstances, the amyloid-beta producing cleavage is sufficiently regular to produce amyloid-beta at high concentrations. The amyloid-beta form into toxic amyloid groups, called oligomers. At very high concentrations, the amyloid-beta can also form into larger insoluble chains which eventually accumulate into amyloid plaques.

42. The amyloid hypothesis posits that either the oligomers or the plaque are responsible for Alzheimer's. Certain researchers believe that the amyloid plaque causes surrounding neurons to develop intercellular tangles of a protein called tau. The tangles block the neurons' transport system, harming synaptic connections between neurons. More recently, many researchers have come to believe that the oligomers may cause Alzheimer's by diffusing into synapses (the junctions between two nerve cells) and destroying them. Under either version of the theory, the deterioration of synaptic connections caused by amyloid beta oligomers or plaque causes loss of cognition and the other symptoms observed in Alzheimer patients.

43. In the decades after its formulation, the amyloid hypothesis displaced older theories, becoming the leading theory explaining Alzheimer's. Billions of dollars were spent researching potential cures based on the amyloid hypothesis. According to a 2017 review, more than a hundred products were tried or advanced to clinical trials.[4] These products targeted nearly every molecule the amyloid hypothesis suggests may assist in treating or preventing Alzheimer's

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576861/

disease, from molecules that inhibit the gamma secretase and BACE-1 molecules that drive production of beta-amyloid, through monoclonal antibodies that inhibit the formation of beta-amyloid plaque or break it up, to drugs that inhibit other molecules with which beta-amyloid interacts. Yet none succeeded.

44. These failures have taken a toll on the Amyloid-beta hypothesis itself. A growing minority of researchers and practitioners dispute the theory.

B. How Aducanumab Works

45. Aducanumab is a monoclonal antibody, which is a laboratory-made clone of naturally-occurring antibodies.

46. Antibodies are proteins that circulate throughout the body until they find, and attach to, other proteins known as antigens. The antibody thereby draws the immune system cells' attention to the protein, which these cells then destroy.

47. For decades, researchers have attempted to develop products that would target beta amyloid to treat Alzheimer's. All failed.

48. Yet according to Defendants, what the failures showed was that the human body could not safely tolerate the high doses of antibodies necessary if the antibodies targeted *all* forms of beta amyloid. Defendants claimed that Biogen had learned the lesson of these failures. Aducanumab does not target all beta-amyloid. Instead, it selectively targets *aggregated* beta-amyloid, with little or no unproductive binding to beta-amyloid monomers. By more precisely targeting aggregated beta-amyloid, Defendants claimed, Aducanumab can be given in doses high enough to be clinically effective.

49. Beta-amyloid aggregates in two principal different forms, soluble oligomers or the insoluble fibrils which make up plaque. Of these, aducanumab preferentially targets fibrils.

C. The Death and Apparent Rebirth of Aducanumab

> ***"It's make-or-break for the company. I can't think of more of a defining event for a large-cap company."***

-Brian Skorney, Robert W. Baird & Co. analyst, concerning the Aducanumab Advisory Committee Meeting

> ***"So is there any product in any pipeline from any company that can be at par with aducanumab and can compensate for potential failure of such a major product? So I don't think so."***

-Defendant Vounatsos at the J.P. Morgan Healthcare Conference, shortly before futility was declared

> **"[*Biogen] is basically a declining business. In the case of an aducanumab non-approval, it just becomes a very difficult investment story."***

Mohit Bansal, Citigroup analyst, as reported in February 5, 2021 *Reuters* article

i. Death

50. Biogen submitted an Investigational New Drug (IND) Application to the FDA for Aducanumab in 2011 and began Phase 1 trials shortly thereafter.[5]

51. Biogen's first study, Study 101, was a Phase 1, ascending dose study of 53 subjects. Single doses ranging from 0.3 to 60 mg/kg of aducanumab, or placebo, were administered to patients with mild to moderate Alzheimer's disease on a randomized and blinded basis.

52. Biogen used the safety data from Study 101 to inform Study 103, the Phase 1b/2 study that began in 2012 and yielded results beginning in 2014.

53. Study 103 (sometimes known as "PRIME") included a 12-month randomized, double-blind, placebo-controlled period, followed by a dose-blinded long term exposure period.

[5] Because aducanumab is a biologic, Biogen must file a Biologics License Application (BLA) for its approval. But the clinical trials that lead to a BLA are the same as those that lead to a New Drug Application (NDA).

A total of 196 participants at 27 clinical locations across the United States were randomized and dosed.

54. The subjects were aged 50 to 90 years and had early symptomatic Alzheimer's disease and PET-confirmed brain amyloid pathology.

55. A particular form (or allele) of a gene that codes for the production of apolipoprotein E ("ApoE"), a protein, is associated with higher rates of Alzheimer's. Each person inherits two forms of ApoE, one from each parent. Having one ApoE ε4 gene ("APOE4") (25% of the population) increases the risk of Alzheimer's disease; having two (2-3%) increases the risk even further.

56. APOE4 is a risk factor, not a death sentence, because not everyone with APOE4 develops Alzheimer's, and not everyone with Alzheimer's has APOE4 genes. Still, APOE4 is a potent risk factor. Even though only about one quarter of the population has at least one APOE4 gene, almost half of all Alzheimer's patients do.

57. APOE4 carriers are also at an increased risk for amyloid-related amyloid imaging abnormalities (ARIA), including ARIA-E. Because ARIA is a known side effect of anti-amyloid beta monoclonal antibodies like aducanumab, APOE4 carriers were potentially at high risk, particularly when given higher doses.

58. Study 103 included both APOE4 carriers and noncarriers. One cohort, which consisted solely of APOE4 carriers, was designed to assess whether the incidence of ARIA could be mitigated in APOE4 carriers through titration.[6]

[6] Drug titration is the process of adjusting the dose of a medication for the maximum benefit without adverse effects. When a drug has a narrow therapeutic index, titration is especially important, because the range between the dose at which a drug is effective and the dose at which side effects occur is small.

59. Study 103's primary endpoint was the safety and tolerability of aducanumab. Secondary endpoints were (1) the effect of aducanumab on brain amyloid content; (2) the pharmacokinetics of aducanumab; and (3) the immunogenicity of aducanumab. Included as exploratory endpoints were measures of clinical efficacy, including change from baseline on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) and Mini-Mental State Examination (MMSE) tests. Both CDR-SB and MMSE were later used as endpoints in Biogen's Phase 3 trials.

60. According to Biogen, four major findings from Study 103 influenced the design of the two Phase 3 trials that would begin in 2015: (1) Biogen identified 10 mg/kg as the most efficacious dose of aducanumab; (2) Biogen found the CDR-SB scale to be sensitive enough to detect changes among early symptomatic Alzheimer's patients; (3) Biogen observed greater variability on the CDR-SB among patients with more advanced disease at baseline; and (4) in 2016, Biogen concluded that titration did lower the incidence of ARIA in APOE4 carriers as compared to fixed dosing.

61. On September 28, 2015, Biogen reached a Special Protocol Assessment ("SPA") Agreement with the FDA on the design for Phase 3 clinical trials.

62. An SPA is an agreement through which the FDA concurs with certain specific critical elements of a clinical trial's design, such as entry criteria, dose selection, planned statistical analysis and endpoints. The FDA's guidance on the SPA process explains that reaching SPA Agreement does not mean that the FDA agrees with every detail of trial protocol, does not mean that the FDA will accept a new drug or biologics license application, and does not mean that the trial results will be adequate to support approval. Instead, it means the FDA will consider itself bound as to the specific issues to which it agreed in the SPA. In general, if the clinical trial adheres to the SPA and the results are statistically significant according to the statistical analysis

plan agreed to by FDA, assuming other aspects of the application are satisfactory (such as safety, PK and Chemistry, Manufacturing and Controls), it is expected that FDA will approve the NDA or BLA.

63. Study 301 and Study 302 were identical global randomized double-blind, placebo-controlled parallel Phase III studies designed to show aducanumab's safety and efficacy. These two Phase 3 trials included an 18-month double-blind placebo-controlled period, followed by a dose-blinded long term extension period.

64. Together, Studies 301 and 302 enrolled 3,285 patients at 348 sites across 20 countries. Participants were between 50 and 85 years of age, with early symptomatic Alzheimer's disease, and positive for brain amyloid pathology as assessed by positron emission tomography ("PET"). Per the study protocols, approximately 80% of participants in both studies would have a baseline clinical diagnosis of mild cognitive impairment ("MCI"), and approximately 20% would have a diagnosis of mild Alzheimer's disease dementia, the latter of which denotes patients whose Alzheimer's substantially interfered with daily life.

65. Both APOE4 carriers and noncarriers were enrolled, with APOE4 carriers by design accounting for approximately two-thirds of each study population.

66. The studies' primary objective was to evaluate aducanumab's effect in reducing clinical decline as measured on the CDR-SB.

67. The studies' secondary objectives were to evaluate aducanumab's effect in reducing clinical decline as measured by three other tests, the MMSE, the Alzheimer's Disease Assessment Scale - Cognitive 13-Item Scale ("ADAS-Cog 13"), and the Alzheimer's Disease Cooperative Study - Activities of Daily Living - Mild Cognitive Impairment ("ADCS-ADL-MCI").

68. The studies' tertiary objectives included assessing aducanumab's effect on behavior as measured on the Neuropsychiatry Inventory-10 ("NPI-10"), as well as the safety, tolerability and pharmacokinetics of aducanumab.

69. Clinical measures were evaluated at baseline, 6 months, 1 year, and 18 months.

70. In addition to the clinical measures, various biomarkers were assessed to study the effects of aducanumab on the brain pathology. PET scans were conducted on a subset of patients to determine whether patients receiving aducanumab showed greater reduction in amyloid-beta in their brains than patients receiving placebo, called a biomarker. In turn, Biogen could determine whether removal of amyloid plaque correlated with better clinical outcomes – i.e., whether aducanumab worked as intended.

71. While Studies 301 and 302 were identical in design, they started one month apart, with Study 301 beginning first and remaining ahead in enrollment.

Clinical endpoints

72. Once symptoms become noticeable, patients with Alzheimer's disease experience progressive decline in cognition and brain function. Biogen selected the following five clinical efficacy scales to measure the range of symptoms experienced by patients with Alzheimer's disease. Assessments on these five scales reflect several independent sources of information: the patient, the caregiver, and independent clinical assessors. The total scores on these five scales indicate disease severity, with changes over time reflecting the clinical progression.

CDR-SB

73. The studies' primary endpoint was the change from baseline in CDR-SB ("SB" stands for "sum of boxes") at Week 78. The CDR-SB scale integrates assessments from three

domains of cognition (memory, orientation, and judgment/problem-solving) and three domains of function (community affairs, home/hobbies, and personal care).

74. After interviewing the caregiver and examining the patient, the rater assigns a score that best describes the patient's current level in each of these six domains. The "sum of boxes" scoring methodology adds up the scores for each of the six domains, and provides a value ranging from 0 to 18 that can change in increments of 0.5. Higher scores indicate greater severity of Alzheimer's disease.

MMSE

75. The first-ranked secondary efficacy endpoint was the change from baseline in MMSE at Week 78. MMSE is a performance-based test of global cognitive status. The test consists of 11 tasks to assess orientation, word recall, attention and calculation, language abilities, and geospatial functions. The 11 tasks produce scores that are combined to obtain a total score, which ranges from 0 to 30. Lower scores indicate increasing cognitive impairment.

ADAS-Cog13

76. The second-ranked secondary efficacy endpoint was the change from baseline in ADAS-Cog13 at Week 78. ADAS-Cog13 includes both cognitive tasks and clinical ratings of cognitive performance. The test focuses on, inter alia, word recall, ability to follow directions, ability to copy or draw an image, ability to interact with everyday objects, naming, word recognition, memory and concentration. The total score ranges from 0 to 85, with an increased score indicating increasing cognitive impairment.

ADCS-ADL-MCI

77. The third-ranked secondary efficacy endpoint was the change from baseline in ADCS-ADL-MCI at Week 78. In the ADCS-ADL-MCI test, caregivers rate patients' actual

functioning over the previous month on a series of 18 items (ranging from shopping, preparing meals to getting dressed), and assess changes in the functional state of the patients over time. The score ranges from 0 to 53, with lower scores reflecting functional deterioration.

NPI-10

78. The studies' tertiary efficacy endpoint was the change from baseline on NPI-10 at Week 78. In NPI-10, an interviewer compiles an index of the presence, frequency and severity of 10 neuropsychiatric symptoms, including delusions, hallucinations, depression, anxiety and euphoria. The score ranges from 0 to 120, with higher scores indicating more serious symptoms.

Doses Studied

79. The Phase 3 studies compared the effects of two dosing regimens of aducanumab versus placebo over the 18-month placebo-controlled period. Participants were randomized 1:1:1 to aducanumab high dose, aducanumab low dose, or placebo. The randomization was stratified by APOE4 status.

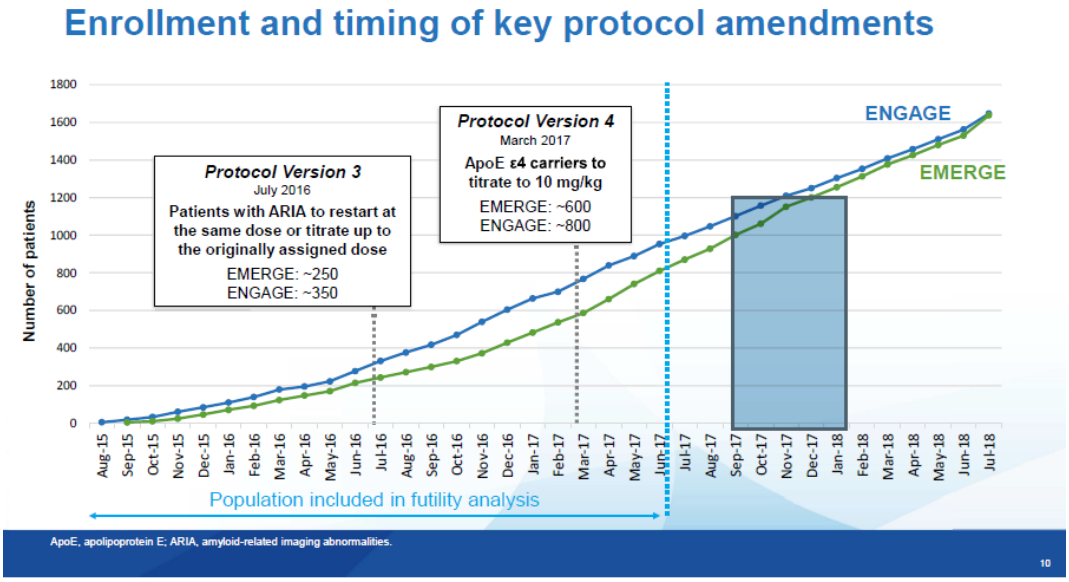
80. Initially, due to concerns about APOE4 carriers' tendency to develop ARIA, both the low and high doses of aducanumab differed based on the participant's APOE4 status.

81. At the beginning of the studies, APOE4 carriers assigned to the low dose received 3 mg/kg after titration over 8 weeks, while APOE4 non-carriers assigned to the low dose received 6 mg/kg after titration over 24 weeks.

82. Similarly, at the beginning of the studies, APOE4 carriers assigned to the high dose received 6 mg/kg after titration over 24 weeks, while APOE4 non-carriers assigned to the high dose received 10 mg/kg after titration over 24 weeks.

Amendments

83. Biogen implemented two important amendments to the protocol during the course of the studies, both due to diminishing concern surrounding ARIA as a side-effect of aducanumab.



Timing of Protocol Version 3 and Protocol Version 4

Protocol Version 3

84. The first amendment, Protocol Version 3 ("PV3"), took place in July of 2016 and related to ARIA management.

85. The Phase 3 trials began with an ARIA management program that resembled the one that had been used in Study 103. This protocol mandated suspending dosing under certain circumstances, for example when ARIA was accompanied by mild or moderate symptoms, or when ARIA-E was radiographically moderate or severe. After ARIA was resolved (i.e., disappeared), dosing could be resumed at the next lower dose. These participants were required to remain at that dose for the duration of the trial. For other participants, for example those with more severe symptoms, dosing was discontinued permanently.

86. PV3 made several changes to the protocol. Under PV3, participants who had suspended dosing due to ARIA that was later resolved could resume dosing at the same dose

(rather than the lower dose) and could continue titration to the target dose. In addition, participants with certain severe symptoms could suspend dosing (rather than discontinuing permanently).

87. PV3 therefore enabled participants who had experienced ARIA – almost entirely APOE4 carriers – to continue on aducanumab and reach their assigned target dose of aducanumab.

Protocol Version 4

88. Protocol Version 4 ("PV4") was adopted in March 2017 based on ARIA data from the final enrolled cohort of Study 103 which showed that 10mg/kg doses could be safely administered to APOE4 carriers. With this data in hand, PV4 increased the high dose for APOE4 carriers from 6 mg/kg to 10 mg/kg. The low dose did not change.

89. Thus, after PV4, the high dose of aducanumab, after titration over 24 weeks, was 10 mg/kg for all participants regardless of APOE4 status.

90. PV4 therefore enabled more participants to receive higher doses of aducanumab.

Futility Analysis

91. An interim analysis for futility was included in the Phase 3 study protocol to terminate the studies early if the analysis showed that aducanumab was unlikely to prove effective.

92. The protocol specified that the interim futility analysis would be performed after approximately 50% of participants in the studies had the opportunity to complete the Week 78 primary efficacy assessment. The data cutoff date for the prespecified futility analysis was December 26, 2018.

93. An independent group, external to Biogen and not involved in the conduct of the studies, performed the futility analysis.

94. The prespecified criteria for futility was based on conditional power for CDR-SB, which is the probability calculated on the data at the interim date that the final data would show statistical significance in favor of aducanumab.

95. According to the protocol, the studies would be considered futile if the conditional power pooling both study arms was less than 20%. This meant that if there were less than a 20% likelihood that final study results would be statistically significant in both the low and high dose arms of Study 301 and 302, the studies would be terminated. The conditional power for each study was calculated on a future estimate based on pooled data from Studies 301 and 302.

96. Biogen based its decision to use pooled data on the statistical notion that the pooling approach has better operating characteristics than the single-trial approach, so long as the heterogeneity between the two trials is relatively small. Because the two Phase 3 trials were identically designed, Biogen did not expect significant heterogeneity between the trials.

97. The results of the futility analysis showed that the estimated conditional power values for CDR-SB in the high-dose group was 12% for Study 302, and 0% for Study 301. The probability of a statistically significant difference at the end of the study was therefore well below the prespecified cutoff of 20%.

98. Because the futility criteria had been met, Biogen terminated aducanumab's Phase III trials. In a press release issued on March 21, 2019 announcing the termination, Biogen explained that "[t]he decision to stop the trials is based on results of a futility analysis conducted by an independent data monitoring committee, which indicated the trials were unlikely to meet their primary endpoint upon completion."

99. On this news, the price of Biogen stock fell from its previous close of $320.59 to $226.88, or by over 29%, on March 21, 2019.

100. The analysts who covered Biogen immediately slashed their price targets in response:

Analyst	Price target reduction	Source
SVB Leerink	From $341 to $247	March 22, 2019 report titled *Post-Aducanumab Future Uncertain; Changes Needed But How & When?*
RBC Capital Markets	From $318 to $236	March 22, 2019 report titled *[Biogen] Without Alzheimer's: What's Next and Where Do They Go From Here?*
Morgan Stanley	From $401 to $210	March 22, 2019 report titled *Base Business Risks No Longer Offset By Significant Upside Optionality*
BMO Capital Markets	From $322 to $250	March 22, 2019 report titled *Little Right Now to Cling to*
Wells Fargo Securities	From $455 to $270	March 21, 2019 report titled *Downgrading to Market Perform on Alzheimer's Failure*
UBS	From $395 to $242	March 21, 2019 report titled *The Day After – Where to From Here?*
Oppenheimer	From $375 to $290	March 21, 2019 report titled *Post-Aducanumab, Attention Shifts to Cash Flows*
J.P. Morgan	From $436 to $244	March 21, 2019 report titled *Much Adu About Everything: Failed Phase 3 Futility Analysis Delivers Big Blow to [Biogen]*
Cantor Fitzgerald	From $400 to $250	March 21, 2019 report titled *Increased Risk after [Alzheimer's Disease] Failure*
Canaccord Genuity	From $396 to $275	March 21, 2019 report titled *Aducanumab failure means [Biogen] at a strategic crossroads*
Barclays	From $340 to $250	March 21, 2019 report titled *More Optionality Needed*

101. Analysts made clear that they did not believe Biogen had much of a future without aducanumab.

a. On April 18, 2019, Canaccord Genuity published a report titled *1Q19 preview: what's after aducanumab and other philosophical musings…*

b. On April 24, 2019, a Jefferies analyst published a report titled *Slightly Better Q1, Inventory Impacts – Key is Strategy Post Alzheimer's*

c. On April 22, 2019, BITG published a report titled *1Q19: Life After Aducanumab Looks Complicated*

102. Investors made clear to Biogen that it had to come up with a game-changing new drug or they would head for the exits. As a Jefferies analyst wrote in an April 24, 2019 report:

> Key Takeaway
> Management addressed three issues on the Q1 call: Tec IPR, Spinraza competition, and BD/M&A. Yet the most common investor question we receive relates to the potential for a near-term catalyst to get excited about. Investors who thought there might be near-term "value creation" or "strategic alternatives" were left with nothing to cling to as comments focused on continued [stock] buybacks and long-term pipeline diversification.

103. Many analysts feared aducanumab's failure left Biogen dead. J.P. Morgan made Biogen the first profile in its *The Excavator* series of reports on companies that seemed to be heading to extinction. As J.P. Morgan began its 100+ page report:

> So what does the future hold [for Biogen]? First and foremost (and maybe most obvious), the outlook for top-line growth appears challenged, with MS, SMA, and royalty revenue all at risk and a lack of exciting, de-risked pipeline candidates ready to step up. Secondly, it's clear from our conversations that investors are waiting for Biogen to bring in some late-stage assets with tangible value; however, for a number of reasons (willingness, cost / availability of targets, etc.), this could be an uphill battle and may never even materialize (sometimes you just have to trust what you see). Further complicating matters – at least for the short term – is the lingering uncertainty around Tecfidera IP. With all of this on the horizon, we struggle to get constructive on the name and believe that the onus is on management to change this dynamic.

104. J.P. Morgan's *The Excavator* report on Biogen was published on October 9, 2019 – three weeks before Biogen brought aducanumab back to life.

105. During the Class Period, investors were laser-focused on aducanumab. In a note sent to clients on or about April 21, 2020, an analyst employed by Jefferies wrote that "[f]or every question related to fundamentals, we get 10 questions on Alzheimer's status."

106. In a report dated July 8, 2020, a J.P. Morgan analyst wrote that "with mounting pressures on the core MS/SMA franchises lowering [Biogen]'s perceived floor valuation, everything appears to be riding on this single, controversial asset [aducanumab]."

107. And in a November 3, 2020 article, a Wolfe Research analyst wrote: "By our modeling at least, [Biogen] lives and dies by how aducanumab plays out. This is because [Biogen]'s underlying revenue base is like quicksand due to patent expiries and competitive threats."

ii. The Apparent Rebirth

108. Faced with a declining future, Defendants refused to accept aducanumab's failure.

109. As an SVB Leerink analyst noted in an April 24, 2019 report following the futility analysis, Biogen "did not commit to ending their quixotic investment in anti-amyloid approaches for Alzheimer's".

110. Biogen continued to collect data between the December 28, 2018 futility cut-off and its futility declaration on March 21, 2019. According to an October 23, 2019 Bloomberg article, Biogen then tasked ***49*** of its statisticians to pore over the Phase III results and salvage any data that could support aducanumab's approval.

111. In clinical trials, the statistical analysis plan must be determined before the trials begin and the final determination of efficacy must be made based on the pre-specified clinical endpoints as analyzed in the pre-specified statistical analysis plan. Hunting through the trial data and running statistical analyzes after the fact is *usually* considered unreliable and a form of data manipulation.

112. Data from clinical trials, or any statistical study for that matter, can be analyzed in multiple ways. The practice known as "p-hacking" occurs where researchers try multiple analysis

to yield a desired result. The "p" in p-hacking refers to the "p-value," a statistical measure that shows, the probability of the study results by chance alone if no drug effect was present. The American Statistical Association ("ASA") defines a p-value as "the probability under a specified statistical model that a statistical summary of the data (*e.g.*, the sample mean difference between two compared groups) would be equal to or more extreme than its observed value."[7]

113. For example, in the context of clinical drug trials, tests of a drug intended to treat a certain disease may show that the incidence of the disease decreased among people who took the drug by a certain rate. The p-value represents the probability of seeing at least as much decreased incidence of disease as the trial showed, if the study drug had no effect. A p-value of 0.05 – by convention, the standard for deeming an effect "statistically significant" – means such a result would happen only 5% of the time.

114. What the p-value does ***not*** demonstrate is whether the drug actually had the intended effect, or to what extent it was effective. Rather, the p-value attempts to measure only how surprising the results would be if the drug were not effective.

115. By running multiple post-hoc analyses, a researcher can all but guarantee a statistically significant result. Just as someone rolling a twenty-sided dice will eventually roll a 20, researchers who run different post-hoc analyses on the population will eventually find one that shows the drug "worked".

[7] Ronald L. Wasserstein, *ASA Statement on Statistical Significance and P-Values*, The American Statistician, Volume 70, Issue 2, at 129-133 (2016), *available at* https://amstat.tandfonline.com/doi/full/10.1080/00031305.2016.1154108#.YHc4B-hKg2w ("*ASA Statement*").

116. To close the door to such manipulation, whether intentional or merely reflecting wishful thinking, in the United States, clinical trial endpoints must be specified, and posted on www.clinicaltrials.gov, before the trial begins.

117. By proposing and running new statistical analyses of its clinical trial results after the data was in, Biogen risked reintroducing the opportunity for manipulation.

118. Biogen's 49 statisticians ultimately "found" the result it demanded.

119. In May 2019, Biogen presented the results of its post-hoc analyses to the FDA's Office of Neuroscience and sought a meeting. The office, headed by Dr. Billy Dunn, held a meeting with Biogen on June 30, 2019. The office of neuroscience concluded that "it would have been more appropriate if futility had not been declared for those studies." After noting that "the effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses is a matter for further detailed consideration," the minutes further noted, "on face, that the effects of aducanumab in that [302] study might not only be interpreted as being supportive of the efficacy of that compound in Alzheimer's disease, but might also be considered exceptionally persuasive on several of the instruments used to evaluate efficacy." The minutes noted "[f]urther complicating the interpretation of the available data for Studies 301 and 302 are the partially conflicting results … for Study 301 as compared with those for Study 302, with particular attention to the discordant high dose results of each study (while noting an apparent degree of consistency of the low-dose results between the studies). A detailed understanding, informed by plans for further analyses [] of the overall results, and especially these discordant results, is critical to any consideration of whether Study 302 (with or without possible support from Study 301, as might be determined from further explorations of the data) might provide

evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease."

120. Having secured Dr. Dunn's office's blessing, Biogen's army of statisticians had no trouble finding some statistical reason to ignore Study 301's results.

121. Biogen requested another meeting with the office, which was scheduled for October 21, 2019. The minutes to this meeting eventually provided that "[t]he analyses conducted since the June 14, 2019, Type C meeting, have established not only that the results of Studies 301 and 302 are interpretable, but on face, suggest an understanding of the discordant results of Studies 301 and 302 sufficient to allow for independent consideration of whether Study 302 might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease."

122. On October 22, 2019, Defendants announced aducanumab's apparent rebirth.

V. DEFENDANTS' FALSE STATEMENTS

A. Defendants Made Misleading Statements Undermined By the Data They Concealed

i. *Defendants' Explanation That APOE4 Carriers Needed A Sufficient Number Of 10mg/Kg Doses Provided By PV4 Makes No Sense Because APOE Carriers In Study 302 Did Not Improve After PV4 And APOE4 Non-Carriers Who Received 10mg/Kg Throughout Both Study 301 And 302 Saw No Benefit Over Placebo, Both Of Which Defendants Concealed*

123. On October 22, 2019, Defendants held a call to discuss Biogen's Q3 2019 earnings and aducanumab's apparent rebirth ("Q3 2019 Call"). Then, on December 5, 2019, Defendants (a) presented aducanumab Phase III clinical trial results at the Clinical Trials on Alzheimer's

Disease ("CTAD") conference ("December 5 Results Presentation"); and separately (b) held a call to answer investors' questions about aducanumab ("December 5 Q&A").

124. There is no precedent for the FDA to approve a drug where one arm of Phase III trials was positive, and the other was negative, unless there is a reasonable explanation for the failure. As an October 29, 2019 report by an analyst employed by RBC noted:

> 3 key things need to happen for adu approval.
>
> []
> 2. FDA/EMA would need to buy into rationale for ENGAGE failure and be convinced EMERGE reflects adu's real activity.

125. And as the FDA itself would later note, the analyses Biogen ran:

> [W]ere not aimed at obtaining independent support from Study 301. Study 301 was a negative study. The purpose of these analyses is to provide maximum understanding of the partially discordant result ***and to determine if this understanding precludes independent consideration of Study 302.***

126. Simply finding a group of patients who performed well in Study 301 does not undercut the negative efficacy results of Study 301. In the Texas Sharpshooter Fallacy, a gunman fires a rifle into a barn, paints a target around the bullet hole, and claims to have hit a bullseye. The fallacy is widely appreciated in the statistics of clinical trials, because the sharpshooter resembles a researcher trying to find statistically significant groups after an experiment is conducted. Data in clinical trials can be sliced in any number of ways, some of which are bound to display statistically significant differences by sheer chance. For example, patients with red hair might have statistically significantly better outcomes. That Biogen can find such a group is not evidence of a real difference; red hair does not make aducanumab work better.

127. Defendants' explanation of the reason for Study 301's failure is post hoc, so they cannot paint the bullseye and then shoot. The FDA's all-but-universal response to clinical trials

with one failed and one successful arm is to ask the sponsor to run another trial. Here, though, Biogen told investors that the FDA would allow it to obtain approval on the basis of Study 302 alone – if Biogen could explain why Study 301 failed so that the FDA did not have to take its failure into account.

128. The FDA's abandonment of its own standards raised concerns among the medical profession. To avoid stretching the FDA's credibility beyond where it was willing to go, Biogen would have to provide a convincing explanation. At a minimum, the explanation of Study 301's failure must be internally consistent and also consistent with the results of Study 302.

129. Defendants told investors they had just such an explanation. They purported to identify a subset of patients in Study 301 whose average scores on endpoints were numerically similar to those of patients in Study 302: Study 301 patients who received a sufficient number of 10mg/kg doses. As Defendant Sandrock told investors on an October 22, 2019 call to discuss Biogen's Q3 2019 earnings and aducanumab's apparent rebirth:

> ***Our primary learning from these data is that sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints. This reduction in clinical decline was statistically significant in EMERGE, and we believe that patients – that the data from patients who achieved sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE.*** After consultation with the FDA, we believe that the totality of these data support a regulatory filing. Importantly, patients included in the futility analysis were those who had enrolled early in the trials and those early enrolling patients had a lower average exposure to aducanumab in large part due to two protocol amendments that occurred sometime after the start of the trials. ***These two protocol amendments were put in place precisely to enable more patients to reach high dose aducanumab, and for a longer duration. As a consequence, the larger dataset available after trial cessation included more patients with sufficient exposure to high dose aducanumab.***

130. On the same call, Defendant Sandrock stated:

> ***So in other words, what I'm saying is that there is a very sort of sharp dose response, if you will, you have to get to high dose of aducanumab and intermediate dosing at least in an 18-month trial is not enough.***

131. Defendants' statements were misleading. As further alleged below, the subgroup analysis that Defendants concealed from investors conclusively refuted their claim. In Study 302, there was no difference in clinical outcomes between APOE4 carriers who received the 6mg/kg dosing (pre-PV4) and those who received the full 10mg/kg (post-PV4).[8] Thus, Sandrock's explanation that receiving a sufficient number of 10 mg/kg doses produces a positive clinical outcome – and conversely not receiving a sufficient number is the reason patients in Study 301 had negative clinical outcomes – is not true. Further, APOE4 non-carriers consistently received 10mg/kg throughout the trials. Yet there was no more than a de minimis difference in clinical outcomes between high-dose APOE non-carriers and placebo – about 0.066 points on the 18-point CDR-SB scale. Thus, sufficient exposure to high dose aducanumab does not reduce clinical decline. Even more, in Study 103, the clinical outcomes of APOE non-carriers were better than those of APOE carriers – the opposite result from Study 302.

132. Defendants also claimed that cumulative dose was important for efficacy. Defendant Budd Haeberlein stated on the Q3 2019 earnings call that "***dosing is a complex combination of duration, magnitude and no interruptions.***" Defendant Budd Haeberlein added that "***you need to achieve high dose for long enough, but also have no interruptions, and so that's a more complex calculation between the two studies.***" Defendant Sandrock likewise stated:

> I think that dose suspension in the context of an 18-month study was – it could be problematic, ***because they didn't achieve enough of the high dose***. But in clinical practice, we don't do 18-month treatment periods. We're going to treat patients

[8] Patients who consented to PV4 before week 16 of their treatment had the opportunity to be titrated to 14 doses of 10mg/kg. Thus, pre- and post-PV4 refers to those patients who adopted PV4 on or before their week 16.

> for longer periods of time. And in that situation I think dose suspension may be acceptable in some patients.

133. Defendants' claim was not true. In Study 302, the number of 10 mg/kg doses the patients received and the total dose did not matter at all. In fact, patients whose treatment was interrupted by ARIA and who therefore received fewer 10mg/kg doses saw better clinical outcomes in both Study 301 and Study 302.

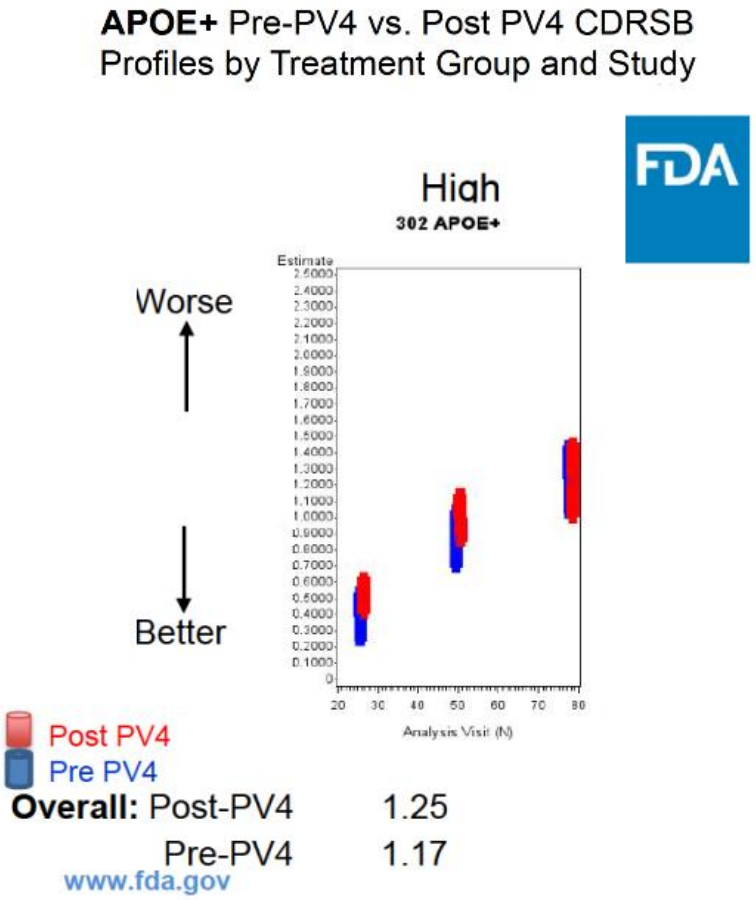
134. Defendants' explanation of Study 301's failure is a story they invented to exploit the fact that they were able to find a subgroup of patients in Study 301 who had experienced better clinical outcomes. The facts Defendants withheld showed that their explanation was not true. Defendants would seek FDA approval of aducanumab with one positive study and one inexplicably negative study.

Defendants' Explanation that 10mg/kg Is the Effective Dose Is Not Consistent With Study 302

135. Biogen applied PV4 in both Studies 301 and 302. The effects of PV4 in Study 301 should be consistent with the effects in 302.

136. *First*, because in Defendants' explanation the dose matters, APOE4 carriers should experience better clinical outcomes on average after PV4 ***in both Studies 301 and 302***.

137. But APOE4 carriers did not experience better clinical outcomes in Study 302 after PV4.

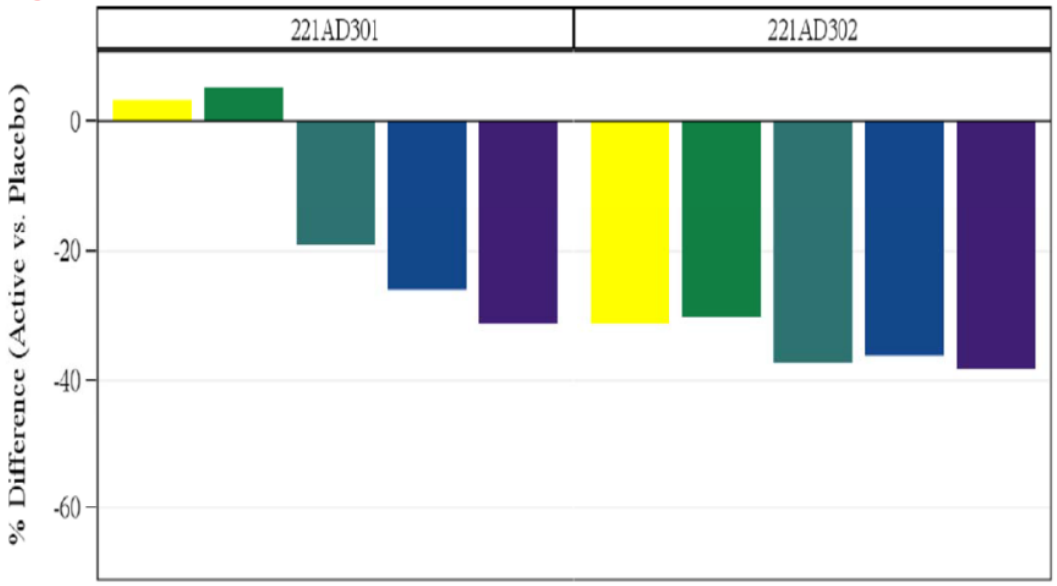


138. In fact, in Study 302 – the purportedly positive study – APOE4 carriers' absolute CDR-SB scores slightly *worsened* after PV4. In Study 302, before PV4, the mean CDR-SB decline in APOE4 carriers was 1.17 points. After PV4, the mean decline rose to 1.25.

139. *Second*, under Defendants' explanation, cumulative dose matters. So in Study 302, patients who receive more 10mg/kg doses should experience better clinical outcomes on average than patients who receive fewer such doses.

140. Yet, in Study 302, whether a patient received 6, 8, 10, 12, or 14 doses had no impact on CDR-SB scores.

Figure 13 Bar plot of CDR Sum of Boxes Adjusted Mean Change from Baseline Percent Difference from Placebo at Week 78 by Number of 10 mg/kg Doses, with Placebo Selected by Propensity Score Matching - ITT Population that have had Opportunity to Complete Week 78 by 20Mar2019: Placebo-controlled Period Excluding Data after 20Mar2019 – Nested Categories



Number of subjects and Adjusted mean at Week 78

Placebo	202	185	157	129	77	220	201	177	144	98
	1.42	1.36	1.49	1.54	1.58	1.56	1.45	1.54	1.38	1.41
BIIB037	202	185	157	129	77	220	201	177	144	98
	1.45	1.43	1.21	1.14	1.08	1.07	1.02	0.97	0.89	0.87

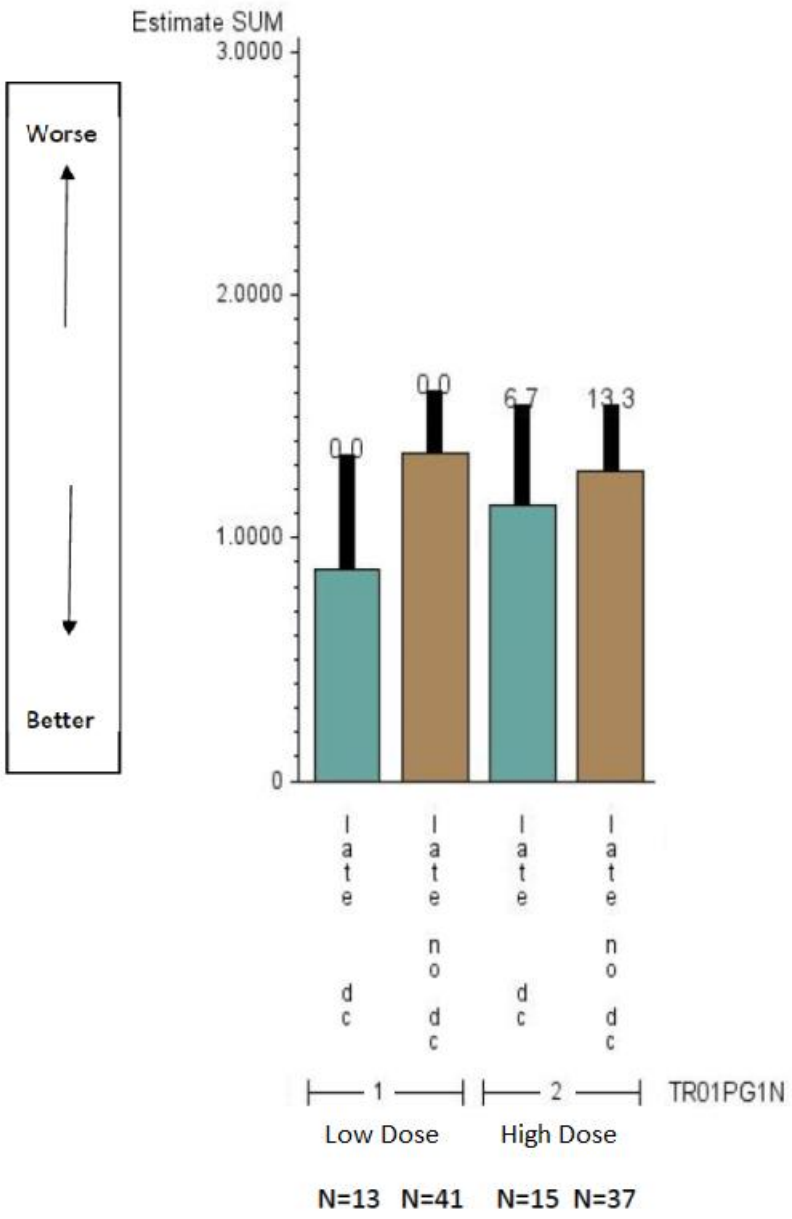
NOTE 1: Covariates in propensity score model include laboratory ApoE status, age, sex, baseline clinical stage, baseline scores of CDR-SB, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, years of education, years since first AD symptom, AD symptomatic medication use at baseline, US/non-US and enrollment window of every 200 subjects. Placebo and treated subjects matched exactly on laboratory ApoE status. Subjects with undetermined laboratory ApoE status are grouped in the randomized ApoE subgroup.

NOTE 2: Results for each threshold were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

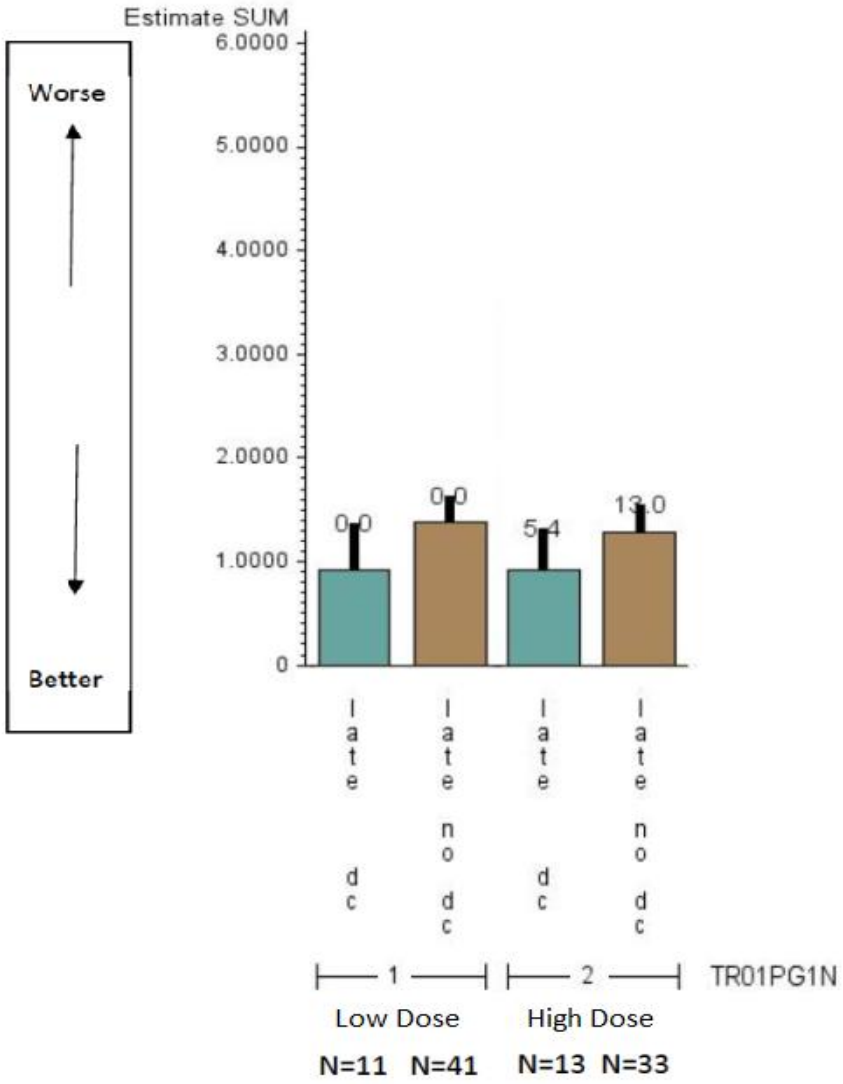
141. As Massie noted, "the number of 10mg/kg doses doesn't matter in study 302."

142. *Third*, patients whose titration to 10mg/kg was interrupted by ARIA did not receive the full fourteen 10mg/kg doses. Because the cumulative dose is supposed to matter under Defendants' explanation, these patients with dose interruptions should experience worse clinical outcomes on average than patients whose dose was not interrupted. Yet in both Studies 301 *and* 302, patients whose high-dose treatment was interrupted by ARIA and so received *fewer* high

doses performed numerically better than those whose treatment was not interrupted and received more high doses:



Note: earl=Pre-PV4 late=Post-PV4; dc= dose titration slowing or reduction due to ARIA



Note:earl=Pre-PV4 late=Post-PV4; dc= dose titration slowing or reduction due to ARIA

143. These facts suggest that *unblinding*, rather than a treatment effect, accounted for the majority of the effect. Patients who experience ARIA will know it because they will be told as much by their doctors and their titration will be interrupted. ARIA is a side-effect of aducanumab, so these patients will also know that they are receiving aducanumab rather than a

placebo, as will their caregivers. Knowing they received aducanumab rather than placebo may influence their answers to interview questions, either in causing them to believe they performed better or in causing them to answer questions about how they function in the world more favorably. Further, the recognition of their ARIA event may preselect patients willing to remain in the study because they are doing well. Because aducanumab's effect would be minimal even if aducanumab were effective, a significant unblinding effect would easily overwhelm any purported treatment effect.

144. Aducanumab may not provide any benefit to APOE4 carriers, but it reliably increases their risk of ARIA, which is dose dependent. So more APOE4 carriers experienced ARIA after PV4 than before. The better clinical outcomes for patients with ARIA between pre- and post-PV4 may result, at least in part, from higher rates of unblinding.

Defendants' Claim that the 10mg/kg Is Effective Is Not Internally Consistent Because APOE4 Non-Carriers Received Essentially No Benefit From Treatment

145. PV4 increased the maximum dosage APOE4 carrier patients could receive from 6mg/kg to 10mg/kg. PV4 made no difference to the treatment of APOE4 non-carriers or patients receiving placebo. All APOE4 non-carriers on high dose received fourteen 10mg/kg doses during the entirety of the Phase III clinical trials.

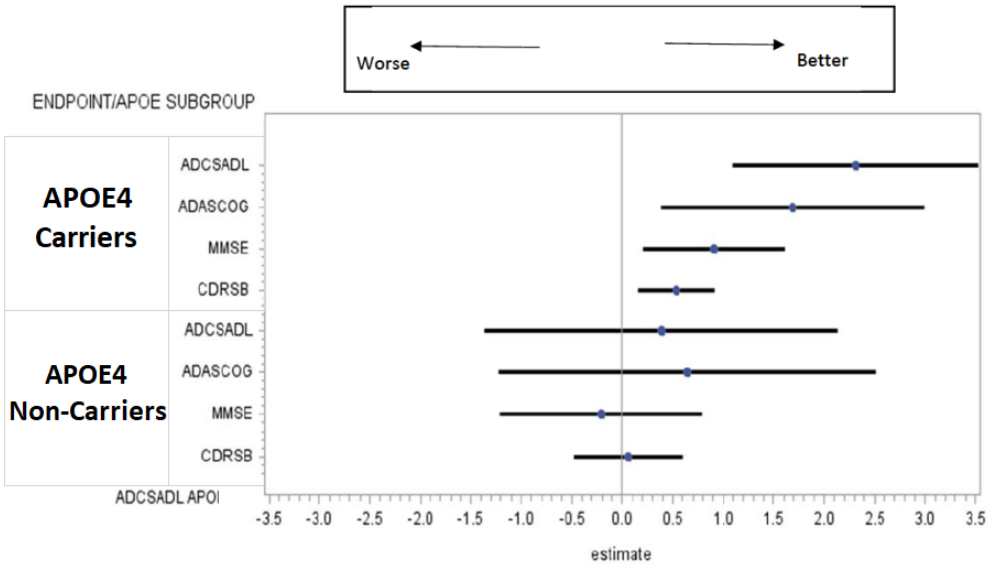
146. Thus, APOE4 non-carriers on average would be expected to experience more favorable clinical results on average than APOE4 carriers, who were less likely to get the full 10mg/kg dose.

147. Yet the difference in clinical outcomes between high-dose APOE4 non-carriers and the placebo group was not only statistically insignificant, it was virtually nil. Though concealed by Defendants, on average, APOE4 non-carriers' clinical outcomes were better than

placebo by only 0.066 points on the 18-point CDRSB scale – a negligible difference that did not even suggest an aducanumab effect, let alone show one with statistical significance:

Group	Study	Estimated CDR-SB point difference vs. placebo
Non-carriers	Pooled	0.066
	301	0.065
	302	0.067
Carriers	Pooled	0.23
	301	-0.07
	302	0.54

148. Indeed, in Study 302, APOE carriers experienced better clinical outcomes than non-carriers on all endpoints.



149. Further, that APOE4 non-carriers did not see improvements in Studies 301 and 302 is inconsistent with Study 103. There, the difference in CDR-SB scores between placebo and high dose for APOE4 non-carriers (1.63) was nearly twice as high as the same difference for APOE4 carriers (0.88). Thus, aducanumab's Phase III results are not consistent with Study 103, even though Defendants presented Study 103 as supportive evidence to Study 302.

* * * * *

150. In sum, the data Defendants withheld showed that patients who had the opportunity to receive the maximum fourteen 10mg/kg dosing did not form a favored group. Instead, they were a heterogeneous set of patients who happened to experience good outcomes that Defendants arbitrarily combined to tell a false narrative to support approval.

151. When Defendants claimed that PV4 was responsible for the changes without disclosing the underlying data that made their claim impossible, they actually misled investors.

a. In a December 6, 2019 report, a BMO analyst concluded that "[n]ew analyses of both EMERGE and ENGAGE demonstrated how the timing of [PV4] resulted in too few patients in the failed ENGAGE trial to ever achieve sufficient drug exposure. ***As shown on page 3, a[ducanu]mab treatment appears to result in the desired efficacy hurdle in the 'post-PV4' treated population of both studies***[.]"

b. In a December 5, 2019 report, a Cantor Fitzgerald analyst concluded that:

> ***When we look at ENGAGE data (the failed trial), we think that the argument of patients getting lower exposure to high dose does make sense.*** Biogen presented patient data post the protocol 4 amendment, and the outcomes were consistent between EMERGE and ENGAGE studies[.]"

c. In a December 5, 2019 report, a Morningstar analyst concluded that:

> One of the key questions going into the Dec. 5 presentation was whether the one-month difference in trial start dates for Engage and Emerge was big enough that the protocol amendment (allowing patients carrying that ApoE4 genetic risk to take the 10mg/kg high dose) could have prevented the more advanced Engage study from meeting its endpoints.

Biogen disclosed that when this amendment was made in March 2017, Engage had 200 more patients enrolled than Emerge. As a result, fewer carrier patients received the high dose, resulting in 22% of patients receiving all possible 10mg/kg treatments in the Engage study, versus 29% in the Emerge study.

Perhaps most importantly, Biogen provided a helpful analysis of only patients enrolled after the amendment, comparing patients in high-dose and low-dose arms of both studies to placebo patients. Among these high-dose patients, 51% in Emerge and 47% in Engage received all possible 10mg/ml [sic] doses, creating less difference in total dosing. This analysis revealed a 30% reduction in decline in CDR-SB in Emerge and a 27% reduction in decline in CDR-SB in Engage for high-dose patients, which we think shows consistency between the trials and could be enough to support approval.

d. In a December 5, 2019 report, an RBC analyst concluded:

A few notably new datapoints which we believe were incrementally favorable. The most interesting new analysis, in our view, looked at patients post the Protocol 4 amendment [], in which the subgroup of [patients] eligible to potentially receive 14 doses of high-dose (10mg/kg) adu (and who consequently had 32% higher cumulative adu exposure) showed similar favorable CDR-SB benefits (27-30%) and benefits on other endpoints across the EMERGE and ENGAGE studies – helping build BIIB's case that ENGAGE's failure was actually due to the enrollment timing differences relative to the protocol amendments.

e. In a December 5, 2019 report, a Guggenheim analyst concluded that:

[A]nalysis indicated that continuous exposure to high dose aducanumab provided consistent benefits to patients [in EMERGE] (this phenomenon was also present in ENGAGE (see figures below). In this vein, one [Key Opinion Leader] on the panel noted that based on the current dataset, he believed that more consistent exposure to higher doses over a sufficient duration of time could lead to more favorable patient responses.

f. In a December 6, 2019 article, a BMO analyst wrote that:

New analyses of both EMERGE and ENGAGE demonstrated how the timing of a specific protocol amendment designed to achieve target 10 mg/kg dosing for all patients in the high dose cohorts resulted in too few patients in the failed ENGAGE trial to ever achieve sufficient drug exposure. ***As shown on page 3, a-mab treatment appears to result in the desired efficacy hurdle in the 'post-PV4' treated population in both studies[.]***

g. In a February 3, 2020 report, an SVB Leerink analyst concluded:

Our View: We believe aducanumab could be the 1st [disease modifying therapy] approved for treating Alzheimer's, and it would be a significant product in AD.

[]

- ***The high dose arms data are more impressive in the post-PV4 cohort when considering the enhanced treatment effect of [Placebo]-adjusted CDR-SB reductions (EMERGE moved from -23% in ITT to -30% for post-PV4, and ENGAGE moved from 2% in ITT to -27% for post-PV4)***

The SVB Leerink analyst concluded that PV4 caused APOE carriers' clinical outcomes to improve:

- ***Initially, a suboptimal 6mg dose was applied in ApoE4 carriers due to ARIA safety concerns***
- ***After PV4, ApE4 [sic] carriers were titrated up to the 10mg dose to ensure enough exposure, as Biogen figured out that ARIA could be managed via careful dose titration; therefore, the data readouts were complicated by the modified clinical design***

152. Other analysts noted that the APOE carrier/non-carrier subgroup analysis was material to aducanumab's prospects for approval and use:

a. In a December 5, 2019 report, a Cowen analyst noted that "[Biogen] did present a couple of new supportive efficacy analyses, but other subgroup analyses (e.g. APOE) were not disclosed".

b. In a December 5, 2019 report, a Credit Suisse analyst noted that "the lack of insight into how [APOE4] carriers (e.g. post-PV4) perform at high doses could prevent some physicians from prescribing without carrier testing[.]"

ii. Defendants Falsely Told Investors That the Observed Reductions In Amyloid Plaque Were Correlated With Better Clinical Outcomes

153. Biogen claims aducanumab helps treat Alzheimer's Disease by removing amyloid plaque. It is Biogen's theory that removing plaque slows the progression of Alzheimer's Disease.

154. Aducanumab's Phase Ib study, Study 103, reported a statistically significant correlation between the removal of amyloid plaque and better clinical outcomes. This early result thrilled investors, doctors, and patients, because it suggested that aducanumab's mechanism of action might actually ***work***:

a. A Barclays analyst wrote in a January 26, 2018 report:

> Positive aducanumab outlook driven by two factors: Our positive outlook for aducanumab is driven by two general factors we believe distinguish it from many of the other unsuccessful anti-AB antibodies:
>
> []
>
> (2) Long-term, dose-dependent positive efficacy and safety data. At CTAD last year, Biogen presented long-term follow-up Phase 1b aducanumab data, including 36 months

> results from the fixed-dose cohort and 24-month results from the titration cohort. Overall, across both data sets, there was a decline in the amyloid plaque levels in a time and dose-dependent manner; there was also a similar response with regards to the rate of cognitive decline as measured by the CDR-SB and the MMSE.

b. A J.P. Morgan analyst wrote in a February 22, 2019 about a conference call the analyst held with two leaders in the field. The analyst reported that the Director of the Cleveland Clinic Center for Brain Health was excited about aducanumab because: "The PRIME data is the first time we saw a directional concordance in amyloid reduction and clinical endpoints; before you saw slight improvements in cognition but nothing on biomarkers or vice versa."

155. Biogen conducted a substudy within aducanumab's Phase III trials that measured patients' level of amyloid plaque through PET (called PET SUVR).[9] The substudy had two aims: to determine whether aducanumab reduced the amount of amyloid plaque and to determine whether reductions in amyloid plaque correlated with positive clinical outcomes.

156. Defendants correctly reported one of the substudies' conclusions. Defendants noted that the biomarker substudy showed a dose-dependent reduction in amyloid plaque. Defendants then claimed that the reduction showed that aducanumab was having a dose-dependent effect on clinical outcomes. For example, on the October 22, 2019 call, Defendant Vounatsos stated:

> [T]he new analysis of the larger dataset, which was conducted in consultation with the FDA, showed that aducanumab had a dose-dependent effect on the underlying pathology as measured by amyloid-PET imaging ***and reduced clinical decline in patients with early Alzheimer's disease*** as measured by the pre-specified primary and secondary endpoints.

157. On that same call, Defendants Sandrock and Budd Haeberlein stated:

> Q: Great, thanks for taking the question. I guess a follow-up and sort of second question from me. So first one is, you've been talking about exposure and dose a lot. Could you just broadly comment on how many of these patients actually achieved all the factors that you were looking for and how easily you think that will be the case in clinical practice. And I guess, the related question to that is, this dose exposure curve that you're sort of

[9] Biogen also conducted substudies to examine whether aducanumab had effects on other biomarkers but the number of patients studied – 36 – made any conclusions mere speculation.

talking about [Sandrock]. I mean, were there characteristics that were different where the kinetics of the amyloid plaque reduction different in these subgroup of patients with the achievement of tau or amyloid reductions were they significantly different? I'm wondering what you think is sort of biologically happening to account for this steep dose exposure curve (inaudible)?

Defendant Sandrock: These are good questions Matthew and we're still learning as we look at the data, but I would say this, the – even in MCI patient, if you look at the amount of amyloid in the brain, it's tremendous. It took 20 years to build that much up and in the context of an 18-month trial, you have to remove a large amount of amyloid. I think that's what distinguishes aducanumab and BAN2401, is that we can – it's safe enough to achieve the doses that allow us to remove a large amount of amyloid. ***And if you don't remove a large amount, you're not going to get an effect.*** Also there is a lag. You remove amyloid, and then there is a little bit of a lag for the clinical effect. We saw that in PRIME for example, where we did have some amyloid lowering at six months***, but we saw no difference in the clinical outcomes at six months.*** It was – it took the 12-month time period to see – to start to see an effect on clinical outcomes.

So, in addition to a large amount of amyloid removal, I think you need to have a little bit of time for that, for that biological activity to have an effect on clinical outcomes. That's what we see and I would say that if you look at the amyloid-PET results that was on one of the slides and those who had more than 10 doses of 10 milligrams, you can see that the SUVR score is very similar in ENGAGE in that subgroup of patients in ENGAGE to the EMERGE total dataset. So – and so again, what it says is that if you give enough of the high dose, you can achieve a certain amount of amyloid removal and that certain amount is what's required to see the reduction in clinical decline in an 18-month study.

Defendant Budd Haeberlein:

Yes, [Sandrock] just to add to that, on the question of numbers. On the graph that you've just referred to, you got the end numbers. So they were 147 for EMERGE and 116 for ENGAGE in that CDR-Sum of Boxes analysis. But the question you ask of how many patients have the precise criteria? Well there aren't precise criteria. Dose response is not binary. ***And so, given the levels of dose you have a different response and it's a bit of a sliding scale. So we have that exploratory analysis that we disclosed to explain what it is we learned around the importance of dose, but there is no perfect number of doses that are required, it's not binary.***

158. Defendants stated that the difference in plaque reduction "tell[s] the same narrative" as the clinical outcomes:

Q: Within the high dose arm in the ENGAGE study, can you talk about the magnitude of plaque reductions you observed in patients who titrated all the way up to the highest dose versus patients who were stopped at 6mg/kg and I guess, ***does the – does a differential magnitude of plaque reduction in those patients at all tell the same narrative you're seeing on the difference in clinical outcomes?*** []

Defendant Haeberlein: [] So to your first question in amyloid plaque reduction, we do believe that PET measurement of amyloid plaque reduction is a very sensitive tool of dose and ***you've correctly identified that ENGAGE at the high dose is showing a lower***

reduction than in EMERGE and we do believe that that is a clear reflection of the lower doses that were achieved in that high-dosing group in ENGAGE.

159. On October 23, 2019, Defendant Vounatsos was interviewed on MSNBC. On that interview, Defendant Vounatsos stated that the decrease in amyloid plaque was the reason for aducanumab's purported effectiveness:

> Q: So [aducanumab] is a monoclonal antibody that actually is designed to go after beta-amyloid plaques which are seen in some Alzheimer's patients. You're telling me that it actually removes the plaques. ***There was some speculation that maybe that's not it; could be that you get Alzheimer's and the plaques then come about as a result of Alzheimer's, it's not an actual cause.*** You're convinced beta-amyloid is the key to dealing with -
>
> Defendant Vounatsos: More than ever. What we demonstrate is that [aducanumab] who's binding to the right part of the amyloid-beta, the aggregated form of amyloid-beta, is able to erode and eliminate the plaque ***leading to the benefits we see in terms of cognition for the patients. It reduces basically the decline and we can see effects such as on memory orientation, language, but also functionally the ability to take care of oneself.***

160. On the December 5, 2019, Q&A, Defendants even explained the discrepant results between Study 301 and Study 302 by claiming that Study 302 was positive ***because*** more plaque was removed than in Study 301:

> Q: Congrats on the presentation today. So I have a question on the amyloid reduction. How do you think about the amyloid reduction in both trials looking similar yet really yielding different results? And how does this square with your hypothesis that there was a sufficient difference in the trial with – in relation to the protocol amendment – to drive a divergent result?
>
> Defendant Sandrock: So I'll start. And I'm sure [Budd Haeberlein] will have things to add. But I would point out that in the high – in the low-dose group, the reduction was similar between EMERGE and ENGAGE. But in the high-dose group, there was actually a difference. And in fact, [Budd Haeberlein] pointed out the SUVR numbers. Even though the amyloid PET was done in a sub-study, it is such a precise measurement. If you look at the error bars, they're tiny, they almost blend right into the actual symbol. And so the small differences between – ***the difference between EMERGE and ENGAGE actually is significant. And I think [Budd Haeberlein] pointed out this morning that in the EMERGE trial, the reduction was what we had expected based on the PRIME data. But ENGAGE fell short. And that's the reason why we started to focus on exposure because it looked like the amyloid reduction in ENGAGE was not quite what we had expected. And that's what led us down this track of looking at drug exposure.***
>
> Defendant Budd Haeberlein: Yes, nothing to add. Thanks, [Sandrock].

161. Defendant Sandrock further falsely told an analyst employed by Credit Suisse that differences in levels of plaque removal explained the discordant results between Study 301 and 302 and between pre- and post-PV4, as reported in a December 3, 2019 analyst report:

> As part of an explanation for the negative ENGAGE results, [Defendant] Sandrock indicated to us that the amyloid lowering effect in ENGAGE underperformed expectations. He believes that the effect may have been partly responsible for the confounding results (e.g. due to less target engagement). He also said that later enrollers had a different effect than early enrollers.

162. Defendants understood that they risked misleading investors. On the December 5, 2019 Q&A, when one analyst asked for specific data on the correlation between amyloid plaque biomarkers and clinical outcomes in Study 301 and 302 by pointing out that Biogen had previously produced such analyses for Study 103, Defendants acknowledged that the analyst's question was "very important" but did not provide the information. Instead, they misleadingly pointed to Study 103 data which had found a dose-response relationship, knowing that Study 301 and 302 had shown no such relationship:

> Q: Just maybe first, I know in the PRIME data, you had looked at the relationship between plaque reduction and, I think, CDR and both MMSE [two clinical outcome measures] and reported that you saw a moderate correlation there, I think, on a Spearman analysis. If you plot the plaque reduction data from the current Phase IIIs and you look at that irrespective of dose versus CDR, I just wonder if you see a similar correlation.
>
> Defendant Haeberlein:
> [Analyst], thanks for the question. ***And it's obviously a very important one.*** We're really limiting our responses today to the analysis that we have shared this morning.
>
> Defendant Sandrock:
> Yes. And [analyst], you're right. In PRIME, when we looked at people [who] had less than one standard deviation change in amyloid plaque versus those that had greater than one standard deviation change, those who had less than one standard deviation change, as published, did not have a clinical benefit, whereas those who had greater than one standard deviation change did. And so in that study, we did see that correlation referred to.

163. 540 Patients from Study 301, and 442 from Study 302, participated in the amyloid plaque PET substudy. Biogen collected week 78 biomarker and clinical outcome data on about two-third of these patients.

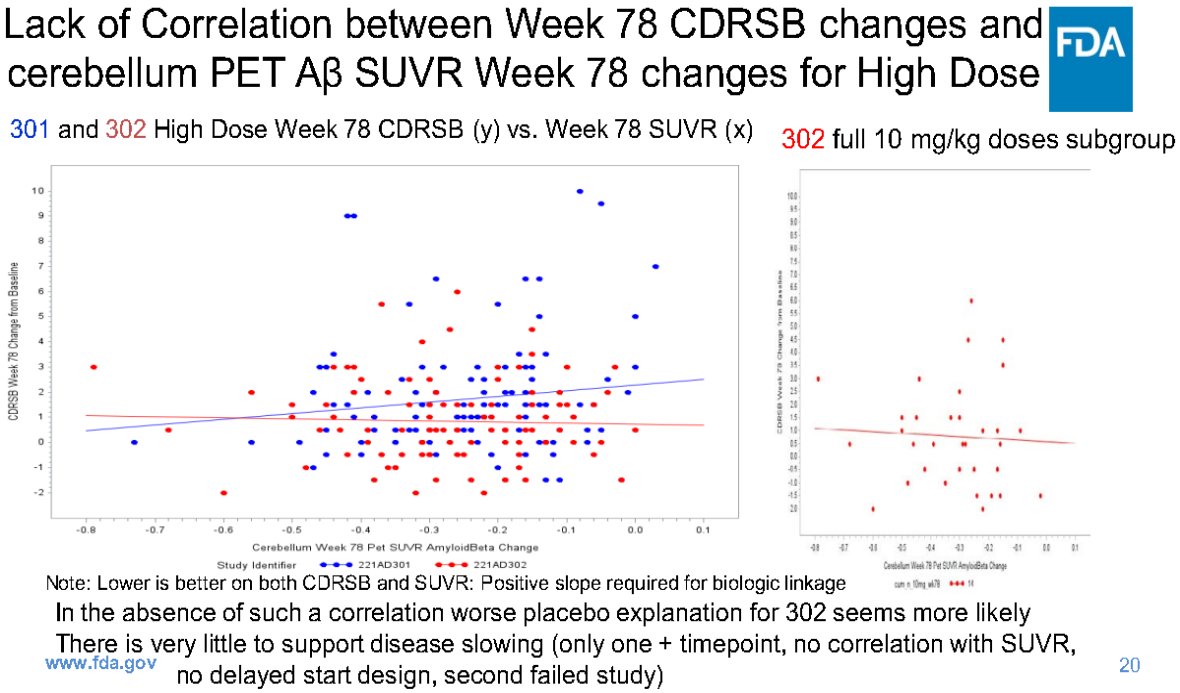
164. The correlation coefficient is the principal measure of the relationship between two variables. The coefficient is a number between -1 and 1. A correlation coefficient of 1 means that for every positive increase in one variable, there is an increase of a fixed proportion in the other. A correlation coefficient of -1 means that for every positive increased in one variable, there is a decrease of a fixed proportion in the other. A correlation coefficient of 0 means there is no relationship between the two.

165. Statisticians use the square of the correlation coefficient (R^2) to measure the proportion of the change in one variable that is explained by the other. Technically, R^2 measures how close observations are to the fitted relationship between the two variables.

166. Neither the correlation coefficient nor R^2 showed a meaningful relationship between amyloid beta levels and positive clinical outcomes. In fact, the correlation coefficient in Study 302 – the successful study – showed a negative relationship between the level of amyloid plaque and clinical outcomes. That means decreases in amyloid plaque levels were weakly associated with *worse* clinical outcomes:

	Study 301	Study 302	Pooled (approximately)
Correlation coefficient between amyloid beta levels and CDR-SB	0.135	-0.035	0.05
Proportion of variation in clinical outcomes explained by changes in biomarkers (R^2)	1.82%	0.12%	0.25%

167. Limiting the analysis to patients who received the full fourteen 10mg/kg doses only increases the negative correlation.



168. As Dr. Massie noted:

> Why don't high dose non-carriers show a clinical effect in Study 302 if they got 10mg/kg earlier, have less ARIA dose reductions and ***if they showed a bigger effect on cerebellum SUVR AB uptake? This seems to call into question whether AB PET SUVR in cerebellum is a surrogate. In fact, within the high dose group, there is actually no correlation between Week 78 change in cerebellum SUVR AB and Week 78 change in CDRSM [sic]. This seems to call into question a disease slowing claim.***

169. Thus, the undisclosed data shows that aducanumab's positive clinical outcomes are not caused by the removal of amyloid plaque. In contrast, it suggests that amyloid reduction does not slow Alzheimer's disease; the amyloid hypothesis ***is not true***. Removing amyloid plaque does not improve clinical outcomes and aducanumab does not work by removing amyloid plaque. As Dr. Jarrow explained in a conversation with a UBS analyst reported in a December 4, 2020 UBS report:

> In the vote that was unanimously kind of positive about effecting [accelerated approval], the pharmacodynamics process of Alzheimer's disease, the caveat was it affected the biomarker, it didn't affect the outcome of the disease. Therefore, the biomarker isn't the surrogate, and that perhaps the field should abandon this as a marker for the disease.
>
> That didn't get translated into some of the press releases that I have seen, and it's been translated into a win. So, if, if you really listen to what the Advisory Committee said, they said, you can't use an accelerated approval using a surrogate, because this isn't a surrogate

> yet. Even though it clearly affected the biomarker, the biomarker had no correlation with the clinical outcome.

170. When they made their October 22 and December 5, 2019 statements, Defendants had already conducted the analysis which showed their statements to be false. As Dunn told the advisory committee, at the June 30, 2019 meeting, the FDA "encouraged the applicant to explore the relationship between exposure, amyloid PET, and clinical endpoints."

171. Defendants' misstatements and omissions of material fact succeeded in misleading investors, as the following statements from analysts and doctors show:

a. Dr. Ronald C. Petersen directs the Mayo Clinic's Alzheimer's Disease Research Center and its Study of Aging. According to Dr. Petersen's biographical page, both focus on neuroimaging and biomarkers. Yet Dr. Petersen was quoted in a December 5, 2019 Washington Post article as saying:

> The million-dollar question in the field has always been, "So what?" If you remove plaque — the insoluble form of amyloid — at this stage of the disease, does it make any difference? Or is that sort of the tombstone of the disease? ***This [aducanumab results] seems to imply that removing the amyloid even at this stage can have a clinical impact.***

b. In an October 29, 2019 report, an RBC analyst noted that "***Internal consistency helps strengthen case for EMERGE being a legitimate [positive] study***: PET biomarker of amyloid also consistent" above a graph showing a biomarker dose response in the EMERGE study.

c. In a December 5, 2019 report, a Credit Suisse analyst related comments made by a doctor with whom the analyst had held a conference call that "in [the doctor's] view, data from the EMERGE trial displayed a meaningful clinical benefit that was correlated with biomarkers."

d. In a December 5, 2019 report, a BTIG analyst wrote that:

> The company reiterated the point we feel is most illuminating: ***plaque removal in ENGAGE was incomplete*** (Exhibit 2). We thought the arguments went a long way to help the discussants dismiss the ENGAGE trial and look for positive segments of the data sets based on full doses.

e. In a December 5, 2019 report, an Oppenheimer analyst wrote that "[t]he favorable clinical results from EMERGE are entirely consistent with dose-dependent changes in key biomarkers including amyloid PET SUVR[.]"

f. In a December 23, 2019 report, an SVB Leerink analyst wrote that a biostatistician with whom they had held a conference call "suggested that the positive association between target reduction (amyloid PET scan and CSF biomarkers) and clinical response in EMERGE would then enable the positive biomarker effect in ENGAGE to be used to support the application."

g. In a February 3, 2020 report, an SVB Leerink analyst reported that they had surveyed physicians, and that in these physicians' views:

- Physicians think the dose-dependent and significant Abeta/p-Tau reductions are in line with aducanumab's clinical efficacy data.

Expressing their own views in the same report, the analysts concluded that the "hook" for aducanumab was its proof of a "[c]lear dose response in Abeta reduction and disease modification effect." The report continued with a header on page 22: "Treatment effect of aducanumab was well correlated with biomarker changes (Abeta and Tau), providing additional data supportive of disease modification." The report concluded that aducanumab was approvable because "[p]ositive association between target reduction (amyloid PET scan and CSF biomarkers) and clinical response should support the use of biomarker data from both trials as additional evidence."

h. In an October 13, 2020 report, the same analyst wrote that:

We believe aducanumab could be the 1st [disease modifying therapy] approved for treating Alzheimer's, and that it would not require an additional trial because…

[]

Aducanumab showed a clear dose-response ***and a consistent association between Abeta/Tau biomarker reduction (dose-dependent imaging results) and clinical response of slowing cognitive decline*** in all completed trials[.]

i. In a November 3, 2020 report, a Wells Fargo analyst wrote:

EMERGE appears as less of an outlier on demonstrating strong correlation between reduction AB PET SUVR and improvements in cognition as measured by CDR-SB and other secondary measures, and the outlier result, requiring explanation may be the failure of ENGAGE to demonstrate improvements in CDR-SB despite statistically significant effect on AB PET SUVR.

iii. Defendants Misleadingly Suggested That Regional Variation Was Not Important

172. On the December 5, 2019 Results Presentation, asked "were there regional differences, country differences, etc.? Can you comment at all on that with regard to the pattern of the results?" Defendant Haeberlein stated:

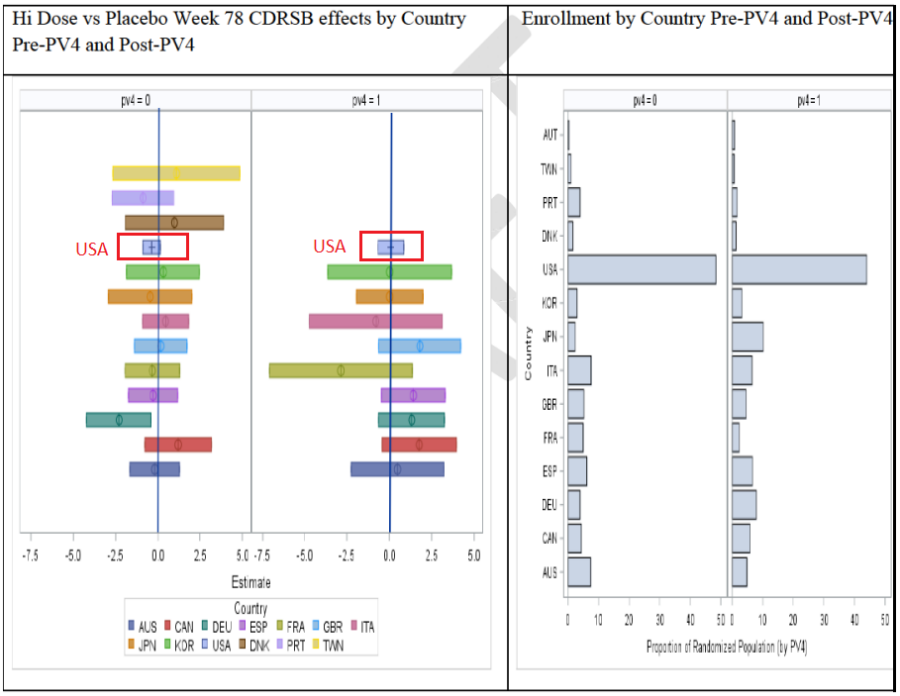
> We're not commenting on how anything at that level may play out. What's important is that, in totality, as we've been discussing in EMERGE, irrespective of region or other slices of the data, the study is overall a positive study.

173. On the December 5, 2019 Q&A, Defendant Haeberlin again claimed that geography did not explain the results:

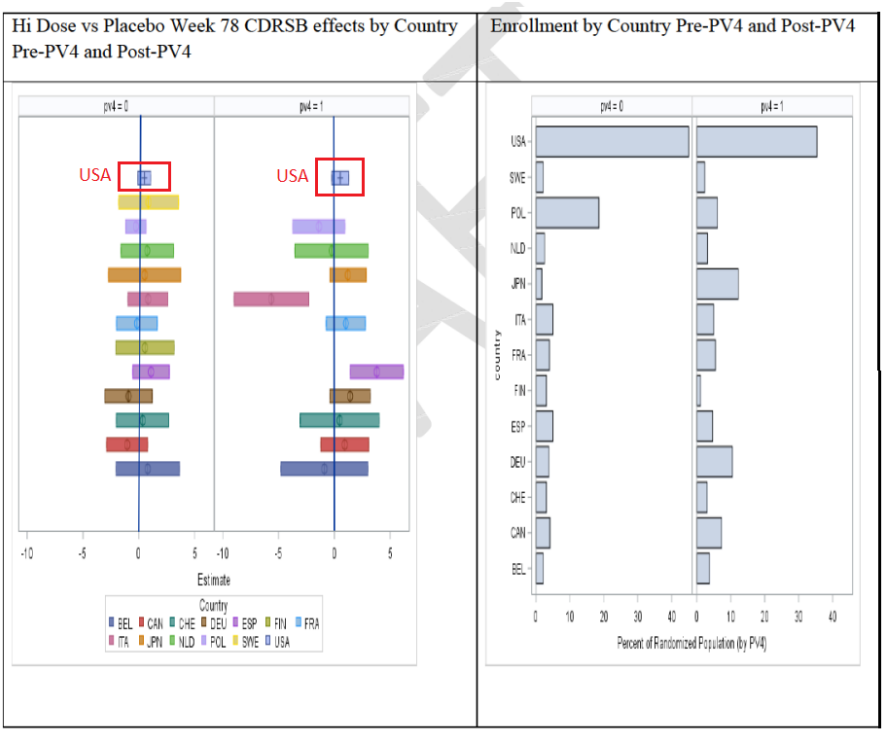
> Q: [] And related to that, are you certain that there isn't anything related to study sites, geography, or any other variation that could explain the breadth of the improvement other than just the exposure?
>
> Defendant Haeberlein: [] And to the second part of your question, we believe, having looked very closely at the baseline demographics and characteristics, that none of these are driving the overall outcomes that we see or the differences that we see between the studies.

174. Aducanumab's Phase 3 clinical trials took place in 20 countries. There were statistically significant differences between countries in the effect of aducanumab in both Study 301 (p-value <0.0001and Study 302 (p-value <0.0001).

175. In the U.S., the treatment effect in Study 301 for the high dose group was negative before PV4 and near-zero thereafter:



176. The treatment effect in Study 302 was marginal both pre- and post-PV4:



177. In the United States, on average, clinical outcomes for patients with the high dose were 0.189 CDR-SB points better than placebo (or substantially less than the average result). Because results vary by country, U.S. patients' poor response was a serious cause for concern.

178. Moreover, the pre- and post-PV4 populations also differed geographically in ways that could explain the results:

a. After PV4, the proportion of high-dose patients from the U.S. dropped by 8% and 13% in Studies 301 and 302, respectively. Moreover, that the difference between placebo and the high dose was even less in the U.S. than overall is concerning given the large country effects.

b. On average, patients who received high doses in Poland experienced worse results than placebo. For example, in Study 302, clinical outcomes for patients with the high dose were 0.26 CDR-SB points worse than placebo in Poland. The proportion of patients in the placebo group who were from Poland dropped from 19.7% pre-PV4 to 5.6% after PV4.

c. In Japan, on average, clinical outcomes for patients with the high dose were 0.5221 CDR-SB points better than placebo (or about double the average result). The Japan population increased from 1.6% pre-PV4 to 12.9% post-PV4.

179. Similarly, though aducanumab is meant to be used early in Alzheimer's progression, the only age group whose performance was statistically significantly better than placebo after PV4 were the over 75. The clinical outcomes for the under 65 age group were worse than placebo. The effect on clinical outcomes for prodromal patients were worse than those on patients had more advanced mild dementia.

iv. Defendants Misleadingly Claimed that the Fact that All Endpoints In Study 302 Were Positive Supported Approval While Concealing that the Reason Was That the Endpoints Were Not Independent

180. Defendants claimed that the fact that Study 302 was positive on all endpoints, rather than just its primary endpoint, gave further confidence that aducanumab worked.

181. For example, on the December 5, 2019 Q&A, Defendant Budd Haeberlein claimed that the "breadth" of endpoints having an effect was "encouraging":

> Q: Congrats on the results. The panel discussion seems pretty intrigued by the functional endpoint. So could you maybe talk about the consistency of the results across various components? Was there any particular component that was driving the delta? Then can you also talk about how the functional endpoints trended in both the studies – specifically after the patients – after you implemented the full commitment – the Protocol 4 commitment?
>
> Defendant Budd Haeberlein: Yes, I'll take the last bit first. We didn't show the secondaries, including the functional endpoint for the Protocol Version 4 population. But the outcomes on those endpoints were consistent for that population. We haven't disclosed the pieces of those endpoints. One thing I would like to say is if you take a look at EMERGE, the primary endpoint, CDR sum of boxes, is comprised of both cognitive and functional components, 3 pieces each. Then the others, MMSE and ADAS-Cog, are more cognitive tests. Then you've got ADCS-ADL, which is a functional score. So it's the breadth of endpoints having on effect on each of these, which is encouraging rather than any one of them or pieces thereof.

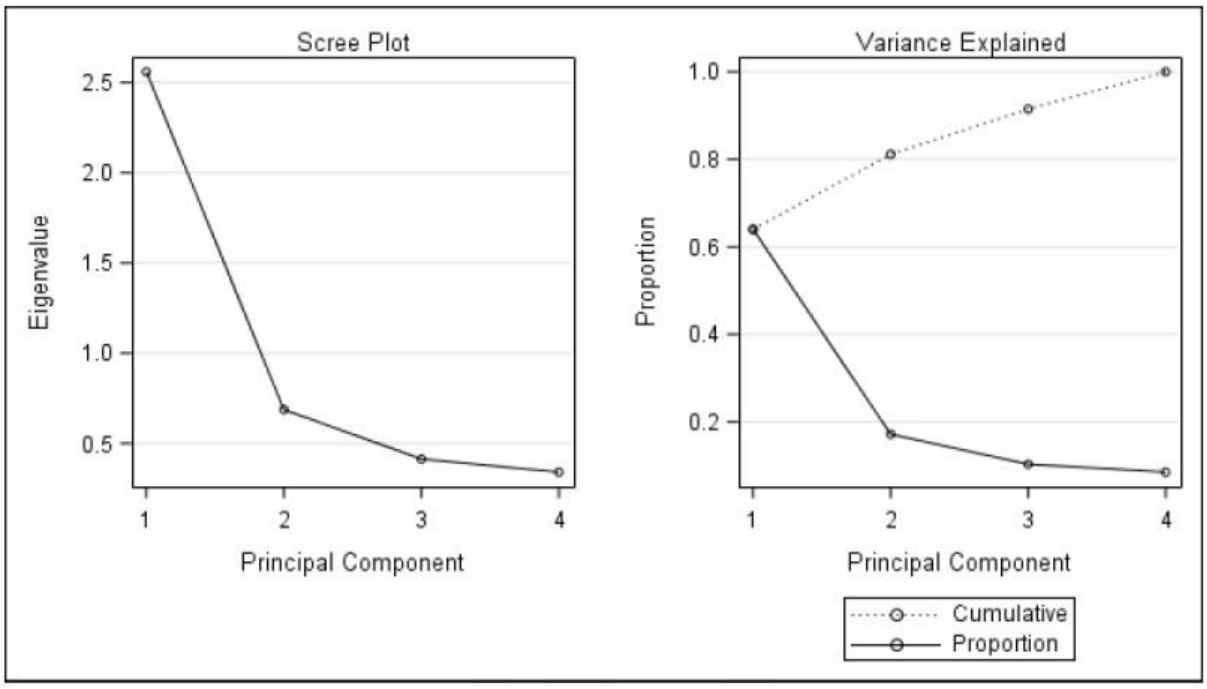
182. That Study 302 was positive on all endpoints is not meaningful because, as shown by the data Defendants concealed, the endpoints are not independent of each other. Rather, scores on all the endpoints are closely correlated. In Study 302, patients who experienced good clinical outcomes as measured by CDR-SB also experienced good clinical outcomes as measured by MMSE, ADAS-Cog 13, and ADCS-ADL-MCI.

Correlation Coefficients				
	CDRSB	MMSE	ADAS-cog	ADCS-ADL-MCI
CDRSB	1.00000	-0.55312	0.49447	-0.64083
MMSE	-0.55312 <.0001	1.00000	-0.58233	0.44297
ADAS-cog	0.49447	-0.58233	1.00000	-0.39773

ADCS-ADL-MCI	-0.64083	0.44297	-0.39773	1.00000

183. Statisticians also use a technique called principal component analysis to determine how many dependent variables are necessary to interpret the results, which they can then plot on scree plots. Here, as the Statistical Review Team noted, "because [the scree plot] levels off very quickly [], it suggests that, rather than four independent factors, one or at most two are needed to explain the variation among the four key endpoints. Therefore, again, the four key endpoints do not measure very distinct efficacy information, i.e. one or at most 2 captures the key information."

Figure 32 Scree Plot of Principal Components of Primary and Key Secondary Endpoints



184. That aducanumab had statistically significant results on all four endpoints in Study 302 says nothing about whether it was effective. Rather, all it shows is that all four endpoints measured the same thing.

185. Yet in a December 23, 2019 report, an SVB Leerink analyst reported on a conference call with an expert biostatistician, who was encouraged that "EMERGE Showed a

strong signal with a positive dose-dependent response across all four independent endpoints that have low correlations."

B. Defendants Repeated Their False Statements

186. On Biogen's earnings call for the third quarter of 2019, held on October 22, 2019, Defendant Sandrock stated:

> **Our primary learning from these data is that sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints. This reduction in clinical decline was statistically significant in EMERGE, and we believe that patients – that the data from patients who achieved sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE.** After consultation with the FDA, we believe that the totality of these data support a regulatory filing. Importantly, patients included in the futility analysis were those who had enrolled early in the trials and those early enrolling patients had a lower average exposure to aducanumab in large part due to two protocol amendments that occurred sometime after the start of the trials. **These two protocol amendments were put in place precisely to enable more patients to reach high dose aducanumab, and for a longer duration. As a consequence, the larger dataset available after trial cessation included more patients with sufficient exposure to high dose aducanumab.**

187. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

188. On the same call, Defendant Haeberlein stated:

> Aducanumab also demonstrated an impact on CSF biomarkers of tau pathology. A statistically significant reduction on CSF phospho-Tau levels was observed in EMERGE and ENGAGE with a dose proportional response in EMERGE. Aducanumab produced a numeric reduction in CSF total-Tau levels in EMERGE and ENGAGE with a dose proportional response in EMERGE. **Although the primary and secondary endpoints were not met in ENGAGE in post analysis,**

> **the subset of patients who received sufficient exposure to 10 milligram per kilogram aducanumab in this case, at least 10 doses of 10 milligram per kilogram showed similar results to the comparable population from EMERGE, in terms of both amyloid plaque reduction and reduced clinical decline on CDR-SB.**

189. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

190. On the same call, Defendant Sandrock stated:

> So in other words, what I'm saying is that there is a very sort of sharp dose response, if you will, you have to get to high dose of aducanumab and intermediate dosing at least in an 18-month trial is not enough.

191. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

192. On the same call, Defendant Budd Haeberlein stated:

> I think what we have learned clearly is that dose is very important, but that if individuals do receive 10 milligram per kilogram then they do have an efficacious response.

193. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

194. Announcing aducanumab's Phase III Topline Results on December 5, 2019, Defendant Budd Haeberlein stated:

> Here is the amyloid PET reduction in ENGAGE. And it looks very similar to what I showed you in EMERGE with a dose and time-dependent reduction in amyloid plaque. However, I would like to point out that in the high-dose group, the delta from placebo was smaller than that we had in EMERGE. And I'm showing that here on the right for comparison. **And indeed, in our Phase Ib PRIME study, we have observed and learned that amyloid PET is quite reflective of the dose that somebody achieves. And so with that understanding, we looked at the difference in dosing of these 2 cohorts. And what you can see is that reduction in amyloid PET difference between the 2 studies is also associated with the difference in dose[.]**

195. The statements were knowingly false and misleading because, for the reasons set out in ¶¶153-170 above, there was no correlation between amyloid beta removal and clinical outcomes.

196. Later in the presentation Budd Haeberlein stated:

> To summarize, the aducanumab Phase III top line results. Following steady termination based on futility, we analyzed a larger dataset. And this showed that in EMERGE, the high dose reduced clinical decline as measured by the primary and secondary endpoints. In ENGAGE, aducanumab did not reduce the clinical decline. **In a post-hoc analysis, data from a subset of patients exposed to the high dose of aducanumab support the positive findings of EMERGE. I'm (going to) read this. In sub studies of biomarkers, aducanumab showed an effect on those disease-related biomarkers.**

197. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

198. Later in the presentation, Budd Haeberlein stated:

> As I mentioned, when we started the studies, we had stratified the dose such that ApoE4 carriers had the lower dose of 6-milligram per kilogram. But from our PRIME study, we had shown that the greatest benefit was at 10-milligram per kilogram. So going into these studies, we did believe that achieving that higher dose would be important for efficacy. But we did not have sufficient information on ARIA to be confident that we could take ApoE4 carriers up to 10-milligram per kilogram. And it was when we received that data in August of 2016 from the titration cohort in PRIME that, that titration itself did lower the incidence of ARIA in exactly ApoE4 carriers. That gave us the confidence. We discussed that with our DSMB. And they agreed that we could safely take ApoE4 carriers up to 10-milligram per kilogram. And I would not recommend changing dose in the middle of a Phase III trial. But it did turn out to be important for this particular study. And if we had not done so, we would not have the results that we have today. So I do believe that we knew dose was important and we made those changes to get to that dose.

199. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

200. On an investor call later the same day, December 5, 2019, Defendant Budd Haeberlein reiterated:

> **Today, though, we shared a new post hoc analysis, which is what we've called those – that subgroup of individuals who were able to have the opportunity for the intended dosing regimen, the so-called Protocol Version 4 group. And in that subset of patients, aducanumab did support the positive findings of EMERGE and ENGAGE.**
> We also shared sub-studies on biomarkers, the robust lowering of amyloid plaque as well as CSF phospho and total tau that we shared before. And we also showed a small tau PET subgroup with statistically significant reduction in tau. I think it's the first time that any antiamyloid agent has shown reduction on a tau PET endpoint.
> **It's also very nice to share that the safety profile was consistent to what we've seen before. And overall, the data that we share, we believe, supports the disease-modifying mechanism of action of aducanumab.**

201. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

202. On the same call, Defendant Sandrock stated:

> Even though the amyloid PET was done in a sub-study, it is such a precise measurement. If you look at the error bars, they're tiny, they almost blend right into the actual symbol. And so the small differences between – the difference between EMERGE and ENGAGE actually is significant. And I think Samantha pointed out this morning that in the EMERGE trial, the reduction was what we had expected based on the PRIME data. But ENGAGE fell short. And that's the reason why we started to focus on exposure because it looked like the amyloid reduction in ENGAGE was not quite what we had expected. And that's what led us down this track of looking at drug exposure.

203. On Biogen's earnings call for the fourth quarter of 2019, held on January 30, 2020, Defendant Sandrock stated:

> Final analysis of these data showed that EMERGE was a positive study with the high dose regimen of aducanumab achieving statistical significance on both the pre-specified primary endpoint of CDR Sum of Boxes as well as on all three pre-specified secondary endpoints.
> On the other hand data from the ENGAGE study did not meet the primary endpoint. **Although we do believe that data from patients who achieve sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE.**
> (Emphasis added.)

204. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

205. On Biogen's earnings call for the second quarter of 2020, held on July 22, 2020, Defendant Vounatsos stated:

> This submission followed ongoing collaboration with the FDA and include data from a comprehensive clinical development program, including EMERGE, the first positive Phase III study ever in this space together with supporting data from the Phase III ENGAGE study and positive results from the Phase Ib PRIME study. Our data show that aducanumab may help to both reduce the decline of cognitive function and help patients' ability to perform certain activities of daily living, which for some patients may result in independence for a longer period of time.

206. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who

received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

207. On the same call, Defendant Sandrock stated:

> I think -- look, the filing is based on these 3 studies, EMERGE, ENGAGE and PRIME. EMERGE is the first study to show in effect, not only on the primary endpoint, but all 3 prespecified secondary endpoints. We believe that data from ENGAGE -- that portions of the data from ENGAGE, a negative study, that portions of it do support the analysis that we did with EMERGE. And then I'll say in also PRIME, which was published, shows even though the clinical endpoints were exploratory endpoints, on the highest dose, there was an effect on MMSE as well as CDR sum of boxes. **And again, very similar that the lower doses did not show much of an effect. So consistent with the findings from ENGAGE and EMERGE, you really need to get to the higher dose. And I think our data are all consistent with that.**
> . . .
> So we submitted all the data from those 3 studies that I mentioned: EMERGE, ENGAGE and PRIME. And what the FDA chooses to look at is – that's their purview. We -- I will say that in terms of the negative study, ENGAGE, we do -- we have analyses that show that those who received the highest dose over a sustained period of time do show evidence of efficacy similar to what we found in EMERGE. And so that's the data we presented to CTAD and AD/PD, and that's why we believe there's supportive evidence coming from ENGAGE.

208. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

209. On Biogen's Aducanumab Phase III Topline Results call, held on April 2, 2020, Defendant Budd Haeberlein stated:

> When we now look at these charts, the top is the pre PV4 population and the bottom is the post PV4 population. We can see the impact of that protocol amendment. In the pre PV4 patients, only 21% in EMERGE and 15% in ENGAGE actually had that dark blue, the full possible 14 doses of 10 milligram per kilogram, whereas post that protocol amendment, there is much less heterogeneity and a much larger proportion of subjects, 51% in EMERGE and 47% in ENGAGE, received those full profitable 14 doses.
> If we then look at the impact of the population who did have the opportunity to receive the full 14 doses, we should compare the original outcome for both studies, and here, I'm showing the primary endpoint CDR-Sum of boxes for both EMERGE and ENGAGE at Week 78, and you will recall that there was a 23% and a 2% difference in those two studies. And if we now look at the patients who had the opportunity for the full 14 doses, in EMERGE, they now have in the high dose a 30% difference versus placebo, and in ENGAGE, where we did not have an outcome in the overall analysis in the PV4 population, the high dose has a 27% difference from placebo. And so in these populations a much more similar outcome can be observed.
> . . .
> So with that, I would like to summarize the aducanumab Phase 3 top line results. Following study termination based on futility analysis of the larger data set showed that in EMERGE high dose aducanumab did reduce clinical decline as measured by both primary and secondary endpoints. In ENGAGE, however, aducanumab did not reduce clinical de[cline].
> **In a post hoc analysis, data from subs of patients, the PV4 population who had the opportunity to be exposed to high dose did support the positive findings of EMERGE. In sub-studies, aducanumab showed an effect on disease related biomarkers both in CSF and in PET imaging studies[.]**

210. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

211. In Biogen's Aducanumab Phase III Topline Results Presentation at the Alzheimer's Association International Conference (AAIC), held on July 29, 2020, Defendant Haeberlein stated:

> In the amyloid PET SUVR group, there was a statistically-significant dose and time dependent reduction versus placebo in both low and high-dose. In the CSF sub-study, there was a statistically-significant dose-dependent reduction in phospho-tau and a numerical difference versus placebo in the total tau.
> In ENGAGE, the primary and secondary endpoints were not met. There was a numerical difference versus placebo in the low-dose group. In the PET SUVR study, there was a dose and time dependent reduction versus placebo, which was statistically significant.
> However, this and the high dose was lower than that, which we've seen in EMERGE and we also understand that the median cumulative dose was lower in ENGAGE subgroup 126 milligram per kilogram versus the EMERGE subgroup at 140 milligram per kilogram.
> **To understand the difference between the studies and the impact of changing the protocol, we defined population by a randomized cohort, who had the opportunity for all 14 doses of 10 milligram per kilogram, and this is termed the post Protocol Version 4 or PV4 population.**
> **If we compare the ITT population with the post-PV4 population, we can see that the post PV4 population in ENGAGE is consistent with the overall ITT population in EMERGE.**
> (Emphasis added.)

212. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

213. In Biogen's Phase III Topline Results Presentation at the 23rd Chinese National Conference of Neurology, held on September 19, 2020, Defendant Budd Haeberlein stated:

> So to go back to the primary results and the primary endpoint for both EMERGE and ENGAGE, as I showed you earlier, CDR Sum of Boxes in the high dose group was 22% difference from placebo in EMERGE and a 2% difference in ENGAGE. If we now look at the post-PV4 population, we have a minus 30% effect in the post-PV4 population in CDR Sum of Boxes in EMERGE and a minus 27% difference from placebo in the ENGAGE population. So essentially in EMERGE, the signal remains whereas in ENGAGE, there was no previous signal.

> However, when patients had the full opportunity for the 14 doses of 10 milligram per kilogram, we do identify a difference from placebo. And here are the line charts of those populations.
> **So in summary, following study termination based on futility, there was an analysis of a larger data set. In EMERGE, the high dose aducanumab reduced clinical decline as measured by both the primary and secondary endpoints. In ENGAGE, aducanumab did not reduce the clinical decline. However, in a post-hoc analysis, data from a subset of patients exposed to high dose aducanumab support the positive findings of EMERGE**. In sub-studies, aducanumab also showed an effect on disease-related biomarkers. (Emphasis added.)

214. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE4 carriers who received 6mg/kg experienced clinical outcomes just as good as APOE4 carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

215. On Biogen's earnings call for the third quarter of 2020, held on October 21, 2020, Defendant Sandrock stated:

> So, look [our] argument rests on the fact that we have a robustly positive study in EMERGE, positive on the pre-specified primary and all secondary end points. We have a supportive study in the Phase 1b trial, which was published in Nature a few years ago. And then we have ENGAGE and we believe we understand why ENGAGE was a negative study. And our belief is that it doesn't detract from the positive study.

216. These statements were knowingly or recklessly misleading, for the reasons set out in ¶¶123-150 above, namely that the different results between pre- and post-PV4 patients in Study 301 was a meaningless statistical artifact as shown by the fact that: (a) in Study 302, APOE carriers who received 6mg/kg experienced clinical outcomes just as good as APOE carriers who received 10mg/kg; (b) in Study 302, the number of 10mg/kg doses patients received had no

impact; and (c) in both Studies 301 and 302, APOE4 non-carriers did not experience any clinical benefit.

VI. LOSS CAUSATION

A. The FDA empanels an advisory committee

217. "When a scientific, technical, or policy question arises, such as whether an unapproved product is safe and effective, FDA often relies on Advisory Committees to provide independent advice." "Committees typically are asked to comment on whether adequate data support approval, clearance, or licensing of a medical product for marketing." "The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making and lend credibility to the product review process." "***Advisory committee meetings often receive considerable media attention, and the agency welcomes such scrutiny because it helps provide public assurance of a responsible process***." [10]

218. It was inevitable that aducanumab would face an advisory committee because the FDA's process badly needed credibility:

a. The potential consequences are immense. If aducanumab is approved, it will be prescribed to hundreds of thousands, perhaps millions, of patients. It will become the only disease modifying therapy for Alzheimer's Disease. It will cost tens of billions of dollars annually and overwhelm the country's PET scan capacity.

b. The data are controversial. Aducanumab's Phase III trials had two arms. One was positive; the other was negative. In any other case, the FDA would have instructed the sponsor to

[10] https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process

conduct another Phase III trial, but here, the FDA seeks to approve aducanumab without any further trials.

c. The history is controversial. Biogen declared futility as to the aducanumab trial. It then declared that it erred in declaring futility.

d. There is significant pushback from physicians. A large number of physicians believe aducanumab should not be approved.

219. Thus, as observers recognized, the decision of the advisory committee was to be a critical factor in the success of aducanumab.

a. In an October 24, 2019 report, an SVB Leerink analyst wrote that "FDA Approval is Likely though Scrutiny from Advisory Committee Seems Inevitable."

b. In a November 20, 2019 report, Cowen analysts wrote that "[a]n advisory committee review for aducanumab is a near certainty. [] It is far more likely that the agency will want to convene a panel review to discuss the unusual efficacy analyses and explain its thinking (positive or negative) before acting."

B. The FDA Releases Effusive Briefing Materials and Buries the Massie Report

220. On November 4, during trading hours, the FDA released briefing materials ("Briefing Materials") for the Aducanumab Advisory Committee meeting.[11]

221. The Briefing Materials included:

a. A report from the FDA and Biogen which, together with Appendices 1 and 2 thereto, ran to 343 pages;

[11] The FDA's guidance provides that the Advisory Committee Briefing materials were shared with Biogen and the Advisory Committee at least 21 business days before the November 6 Advisory Committee meeting. Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members, FDA August 2008, Appendix A, available at https://www.fda.gov/media/75436/download

b. More than 90 minutes of pre-recorded presentations by Biogen;

c. A 50-minute pre-recorded presentation by the FDA's efficacy reviewer;

d. A 7-minute pre-recorded presentation by the FDA's safety reviewer; and

e. A 45-minute pre-recorded presentation by Dr. Massie.

222. On the whole, the Briefing Materials were effusive.

223. For the first time in FDA history, the FDA and a sponsor filed joint briefing materials ("Joint Report"). The Joint Report set out Biogen's position; the FDA inserted short, paragraph-long comments, the majority of which simply said the FDA agreed with Biogen's position.

224. The FDA characterized EMERGE as "highly persuasive" evidence of aducanumab's efficacy.

225. The FDA assumed that EMERGE was a positive study and set about trying to find reasons why ENGAGE was wrong rather than evidence that aducanumab was ineffective:

> A guiding principle of the hypothesis was that if aducanumab is effective and the effect is dose-related as in Study 302, it follows that patients in Study 301 with adequate and consistent dosing should also demonstrate an effect on clinical endpoints.

226. The FDA agreed that Biogen could use a Phase 1b study, Study 103, as a supporting study to approve aducanumab, even though it was an exploratory study.

227. The FDA concluded that "[t]he effect of aducanumab in Study 302 is robust and exceptionally persuasive on several of the instruments used to evaluate efficacy."

228. Appendix 1 to the Joint Report was a clinical review report by Dr. Kevin Krudys. Krudys, who had recently moved to the Office of Neurology, reports to Dunn.

229. The Clinical Review Report concluded that "the applicant has provided substantial evidence of effectiveness to support approval."

230. The Advisory Committee was asked to vote on and discuss certain questions. As Advisory Committee Members themselves would note, the questions were heavily biased in favor of approval. The first voting question required the Advisory Committee to simply ignore ENGAGE. The second asked the Advisory Committee to state whether the Phase Ib study provided support. The third asked the Advisory Committee to state whether Biogen had shown evidence that aducanumab removed amyloid plaque – regardless of whether the removal did anything to reduce cognitive decline in Alzheimer's patients. The fourth asked whether Study 103 and Study 302 supported approval in light of the post hoc analysis of Study 301. Analysts noted that these were leading questions designed to support approval:

a. In a November 4, 2020 report, a J.P. Morgan analyst wrote that "[w]e see the FDA position as highly supportive of approval and believe the questions presented to the panel are structured to reinforce the FDA position."

b. In a November 5, 2020 report, an RBC analyst wrote that the "[d]raft questions [are] clearly designed to steer AdComm panelists favorably."

231. Appendix 2 to the Joint Report, beginning on page 247 of the Briefing Materials, was a presentation by the FDA's statistical reviewers whose principal author was Dr. Tristan Massie ("Massie Report").[12] The Massie Report was dense to the point of being impenetrable. It contained almost one hundred pages of statistical analyses. The analyses were organized by Study rather than topic, so finding the same analysis of Studies 301 and 302 requires sifting through dozens of pages.

232. It was nearly impossible in the short time provided before the close of trading on November 5 for investors to appreciate the Massie Report on its merits. Readers would have to

[12] The Massie Report is attached as Exhibit 1 hereto and is incorporated by reference.

pore over the Massie Report to discover that it revealed shocking new data to which Biogen and the other portions of the FDA had no answer. As further set out above, the Massie Report revealed that: (a) PV4 had no impact on APOE4 carriers in Study 302; (b) the number of 10mg/kg doses had no impact on APOE4 carriers in Study 302; (c) in both Studies 301 and 302, APOE4 carriers whose titration was interrupted by ARIA experienced better clinical outcomes than patients whose titration was not interrupted and so received more 10mg/kg doses; (d) the effects on APOE4 non-carriers was essentially nil; (e) there was no correlation between the amount of amyloid plaque removed and clinical outcomes; (f) there was wide variation in treatment effect between countries and the U.S. performed poorly, while geographic distribution of patients plausibly explained the differences between pre- and post-PV4; and (g) the multiple endpoints were closely correlated. The Massie Report leveled devastating, unanswerable criticisms against the case Biogen made for aducanumab's approval.

233. Analysts focused on the laudatory position the FDA took in the Briefing Materials. Further, several analysts did not mention the Massie Report at all. Thus, it is plain that even analysts whose job was to cover Biogen had not read the Massie Report but had noticed the FDA's clear bias in favor of approval.

a. In a November 4 article which did not mention the Massie Report, a Cantor Fitzgerald analyst reported that "[s]imply put if you look at the documents and see how many times in the FDA position box that they say 'we agree' it suggests that Biogen's key arguments are now well positioned into Friday's AdCom".

b. On November 4, a Guggenheim analyst published a report titled *Adu Briefing Docs Are Out, Draft Questions Sets Up For A Positive Vote; Approval More Likely Than Not*; it did not mention the Massie Report.

c. On November 4, an H.C. Wainwright analyst published a report which did not mention the Massie Report and stated that "[b]riefing documents augur well for Friday's AdCom[.]"

d. On November 4, a Jefferies analyst published a report which did not mention the Massie Report titled *Hot Debate but FDA Clearly Reads Positive on Efficacy, Safety*, which provided that "FDA tea-leaves read much more positive than consensus."

e. On November 4, an RBC analyst published a report titled *FDA Drinks the Adu Kool-Aid, Showing Surprising Openness to Approval Despite Mixed Data; Friday's AdCom Still Key*, which provided "we believe the briefing documents read more amenably than even Street bulls would have expected."

f. On November 4, a Barclays analyst published an article titled *Adu Briefing Documents Highlight Supportive FDA Stance*, which provided "outside of the statistical review team portion (which was buried deep in the Briefing Documents, raised much of the same issues brought up by the Street, and whose conclusions were largely ignored otherwise), this represents the near-best case scenario for [Biogen] shares."

g. A February 5, 2021 article quoted Marc Goodman, an SVB Leerink analyst, as saying:

> There was a special relationship. You could crystal-clearly see it. The briefing documents were unprecedented. I've been doing this job over 20 years and I've talked to people who have been doing it longer, and we've never really seen anything like that before, where the FDA is just working that closely with a company. They went to the [advisory committee] basically saying, "This drug's getting approved."

234. Other analysts published initial reports that noted the laudatory language and ignored or downplayed the Massie Report, but published later reports that reported that Dr. Massie's analyses were devastating.

a. Mid-day November 4 report, a J.P. Morgan analyst published a report titled *To Be Brief ... the FDA Wants to Approve Adu*. The report mentioned Dr. Massie's bottom-line conclusion in passing. In a second report issued that evening titled *A Closer Look at the Adu Briefing Docs and The Tale of Two FDAs* noted that "[o]ur more thorough review was eye opening in terms of conflict of opinions between the FDA reviewers and their statisticians, who are far more negative." The second report sarcastically noted in response to one of the FDA's more egregious moves "Data mine much?" The J.P. Morgan analyst then wrote that it was "surprising" that there were no benefits for APOE4 non-carriers and that it "conflicts with [Biogen]'s hypothesis that high aducanumab dosing leads to a better benefit as non-carriers were always able to dose up to 10mg/kg." Thus, though the analyst's initial review was favorable for aducanumab and its approval, after he had completed a more thorough review he found that Massie's statistical review was far more persuasive .

b. On November 4, a Raymond James analyst published a report titled Briefing Documents: "Do Stats Matter?", which provided that "[t]he briefing documents for aducanumab are a landslide win for [Biogen] and increase the likelihood of aducanumab approval substantially." Raymond James noted that there was a Massie Report which disagreed, but noted that "[i]t's going to take us most of the day to go through it all[.]" On November 5, the same analyst published a second report which provided:

> The effusive briefing documents indicate adu *may* be approved[] [h]owever, we were not persuaded by any new data/analysis that aducanumab actually works. In fact, our conviction that the drug probably doesn't work is increased. Put differently, we completely agree with the statistician who essentially annihilated the pro-aducanumab position put forth by the clinical efficacy reviewer ("***unscientific, statistically inappropriate, and misleading***").
>
> []
> Weak correlation between plaque reduction and CDR-SB. The correlation between plaque reduction [] and the primary endpoint [] has an R^2 value of just 0.13, which calls into question the amyloid hypothesis entirely if it wasn't questioned enough already.

c. On November 4, 2020, a UBS analyst published an article titled *First pass of briefing docs suggest FDA has constructive view – this changes everything*. On November 5, the same analyst published a second report providing:

> ***Clinical Review vs. statistical review – clinical clearly prevails here***
> The experts [consulted by the analyst] noted the stark dichotomy in opinion between the clinical review (favoring approval) and the statistical review (against approval, recommending additional trial. The experts noted that prior to publishing the briefing doc, sign-off at the director office level is required[13] and so the overall conclusion of the docs (stating [Biogen]'s trial results provide evidence of efficacy and support approval) essentially implies the FDA is willing to overcome the statistical shortcoming in light of the positive clinical review.

d. The Director in Chemical Biology & Research in the Novartis Institute for Biomedical Research published an article which provided that:[14]

> The fact that Biogen stock jumped on the release of this document tells you most of what you need to know about the stock market (and about investing in biotech stocks in particular). You wonder how many people even got as far as the statistical review section before hitting the big green Buy button.

235. Indeed, even investors who managed to pore over the dense Massie Report would not know what to make of it. Unlike the other reports, the Massie Report bore a prominent DRAFT watermark. To Plaintiffs' knowledge, no statistical review presented to an FDA advisory committee has ever been identified as a draft. Thus, the FDA's highly positive clinical review and presentation and other indicia suggested that the FDA would give the Massie Report short shrift. This is what a UBS analyst concluded in a November 5, 2020 UBS report which stated that the Massie report was "buried at the end of the documents and seemed superseded by FDA's prior commentary."

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[13] While director sign-off is sometimes required as a matter of office policy, in practice, the directors typically delegate the decision to the heads of offices – here, Billy Dunn, who favors approval.

[14] The report was published on November 9, 2020, but was written before the advisory committee meeting.

236. Because the FDA made it clear it wanted to approve aducanumab and few investors had the time to consult the Massie Report, or understand its findings, Biogen's stock price increased to close at $355.63 on November 4, 2020.

237. Yet on November 5, some investors began to digest and give credence to the information that had been made public, though buried, in Dr. Massie's report. On November 5, Biogen's stock fell to close at $328.90, down 7.5%.

C. The Advisory Committee Votes 10-0 Against Approval

238. The Advisory Committee meeting was scheduled to begin early morning Friday November 6 and continue until after trading closed. That day, shares were halted and would only resume trading on Monday November 9.

239. Late Friday, the Advisory Committee discussed and voted on the FDA's questions. The panel's votes were:

> Question 2: Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's Disease?
>
> Yes: 1 Uncertain: 2 ***No: 8***
>
> Question 4: Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's Disease?
>
> Yes: 0 Uncertain: 4 ***No: 7***
>
> Question 6: Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology [i.e., does aducanumab reduce amyloid plaque]?
>
> Yes: 5 Uncertain: 6 ***No: 0***

Question 8: In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?

Yes: 0 Uncertain: 2 ***No: 8***

240. The cause of the panel's dissatisfaction was the facts revealed in the Massie Report.

241. A panelist, Dr. Caleb Alexander, objected to treating EMERGE as a positive study, because:

> I think even with study 302 there are some reasons for question. One is that there's no correlation between plaque reduction and week 78 outcomes.[]
> Then the last that I'd say is that, once again as pointed out by the FDA's own [statistical] reviewer, there's no consistent effect across subgroups [i.e., APOE4 carriers and non-carriers] in 302, yet one would hope to see this with a strong efficacy signal.

242. Dr. Kesselheim, another panelist, raised the same objection:

> I would have loved to see also a mediator analysis on whether the changes in plaque explain much of the differences in the cognitive endpoints, which is of course the burden of proof. The burden of proof is we targeted the oligomers of the amyloid hoping that that would have an impact clinically, and our question is does that bear up; if it's a strong enough effect? I must say I care more about the clinical aspects [i.e., clinical outcomes] than I do about the pathology.

243. As did a third, Dr. Perlmutter:

> I think we see a lack of correlation between the A-beta change and the clinical endpoint CDR-SB. I think that's a concern.

244. A fourth, Dr. Thambisetty:

> I would point to slide 20 of the FDA statistical reviewer's presentation, where you examine the relationship between change in global brain amyloid burden at week 78 in individuals exposed to high-dose aducanumab and change in the CDR sum of box scores. There really appears to be no relationship either in Study 302 or 301, and this appears to be the case even when the analysis is restricted to only individuals exposed to the 10mg/kg dose.
> I think there are some larger implications of these findings which we are not tasked with discussing today. One of the larger questions relevant to these observations is whether

> lowering brain amyloid burden is in fact the correct target in Alzheimer's disease, but like I said, I think that's beyond the remit of the discussion today.

245. A fifth, Dr. Perlmutter, an expert on PET imaging, stated that "the disconnect or the lack of correlation with the clinical benefit is a real problem."

246. Asked whether Study 103 provided support, Dr. Alexander pointed out that the fact that "contrary to 302, the effect was larger in non-carriers than carriers" "gave [him] pause."

247. Summing up, Dr. Duda, a panelist, stated:

> But I think, all in all, the main -- I think several of us have said it already. Dr. Massie's criticisms just were never addressed in the clinical overview, and there seemed to be a disconnect between different aspects of the FDA reporting that are very difficult for us to draw conclusions from. So in light of that, I think it makes it much more difficult to get where the FDA maybe thought we would go today.

248. Dr. Emerson:

> I'm highly critical of the fact that the FDA presentation today was so heavily weighted to just giving the same conclusions that the sponsor did, and that there was no[] presentation by the statistician who'd done a careful analysis and made many points that I was very glad to see that the committee read.

249. Dr. Kessselheim:

> I also wanted to echo what others have said, to thank the FDA, and the sponsor, and Dr. Massie in particular, for their thorough reviews of the material and very helpful presentations.

250. Dr. Thambisetty:

> I voted no as well for all of the reasons discussed throughout the day, and I'd also like to take the opportunity to thank both the applicant and the FDA for the privilege of reviewing this hugely important work. I'd also add a special note of thanks to Dr. Tristian Massie for a really thorough statistical analysis that was very, very useful.

251. The closely-watched advisory committee publicized and endorsed the significance of Dr. Massie's results as demonstrating that Study 301 and 302 did not show aducanumab effective. Further, the advisory committee was made up of eleven world-renowned experts. Their decision showed to investors that Dr. Massie's analyses were reliable.

252. On November 9, Biogen's stock resumed trading opening at $230.82 per share, and closed at $236.26 per share, down 28.2%.

VII. BIOGEN'S POST HOC ANALYSIS CAPTURED THE HOPES OF AN FDA OFFICE DESPERATE PUSH APPROVAL OF ANY TREATMENT FOR ALZHEIMER'S DISEASE, EVEN ONE THAT DOESN'T WORK

253. Biogen caught the attention of an FDA Office desperately seeking to approve a treatment for Alzheimer's disease. As Billy Dunn, the head of the Office, told the Advisory Committee, "[w]e are highly sensitive to the urgent need for the development of new treatments for Alzheimer's disease." No disease modifying treatment for Alzheimer's has ever been approved. While a few symptomatic treatments have been approved, the latest was in 2004. Twenty-two experimental drugs targeting beta-amyloid have been pursued in the 21st century, but none have been successful.

254. Dr. Dunn was a perfect partner for Biogen. Jonathan P. Jarrow, a surgical oncologist who worked in senior positions at the FDA from 2010 through 2019 and who worked closely with Dunn, describes him as "stubborn": "I've had a lot of experience within Medical Policy and Program Review Council meetings, and [Dunn] gets to a conclusion, and then after you bat down the reasons to support his conclusion, he just finds new ones."[15]

255. Dr. Dunn's office compromised its statistical rigor to push approval of an Alzheimer's Disease treatment. The November 6, 2020 Advisory Committee Members said as much. At that meeting, Advisory Committee Member Dr. Scott Emerson would accuse the FDA of "complicity" with Biogen in putting forth unacceptable statistical analyses and add that he was "very, very, very disturbed by some of the analyses that were considered" by the FDA. Dr. Caleb Alexander, another, would observe that the FDA does "an extraordinary amount of explaining around the contrary findings". Dr. Alexander would also add that "***I have a very hard time***

[15] UBS analyst report dated December 4, 2020.

understanding, after carefully reviewing what I thought was a very well done and well-articulated [FDA] biostatistical review, which convincingly argued the evidence was 'at best compellingly conflicted,' ***how the FDA could conclude that there are substantial evidence of effectiveness****[.]"* Nearly all Advisory Committee members would complain that the FDA "foisted" "biased" leading questions on them designed to support approval of aducanumab.

256. Stock analysts whose job is to evaluate and comment on Biogen as an investment were also struck by the FDA's loose standards:

a. Baird: In a November 2020 note quoted in a November 7, 2020 Biopharma Dive article, Baird analyst Brian Skorney wrote that "[i]t is abundantly clear that whatever relationship FDA [Office] Director Dr. Billy Dunn has with aducanumab, his objectivity is completely lost."

b. BMO: In a November 9, 2020 report, a BMO analyst wrote "Rather than seeking ad-com advice as would be customary, it seemed to us that FDA was instead seeking validation for its unorthodox interpretation of a-mab clinical data. However, the committee would have none of it. Because the two Phase I studies [] were identical and impeccably conducted at the same time, it would be negligent to regard EMERGE as a stand-alone trial while using only favorable retrospectively-derived elements from ENGAGE to support the EMERGE outcome."

c. J.P. Morgan: After the Advisory Committee vote, a J.P. Morgan analyst wrote in a November 8, 2020 report that "we don't at all understand why [the FDA] were so pro-adu in the first place".

d. Morgan Stanley: In a November 6, 2020 report, a Morgan Stanley analyst wrote that "We are frankly perplexed why the FDA held the advisory committee, given it knew its position would be controversial."

e. Piper Sandler: In a November 8, 2020 report, an analyst employed by Piper Sandler wrote that "[W]ith Billy Dunn [] running point, FDA went to great lengths – including in the structure and positioning of the questions – to set the stage for a positive review[]" adding that "it's our opinion that a CRL is the right thing to do."

f. Wedbush: A Wedbush analyst wrote in a November 8, 2020 article wearily titled *We Repeat, Does the Aducanumab AdCom Really Matter? [Hint: No, Don't Think So]*:

> [] Ultimately, the AdCom voted 10-0 (uncertain = 1) the EMERGE ("302") study does not serve as primary evidence of effectiveness of aducanumab in Alzheimer's disease (AD). Since this was the only "successful" study, approval would seem to be at risk. Panelists rightfully objected (in our view) to a range of statistical and clinical trial analyses/conclusions. However, we still pose the question: does this vote even matter? In our view, FDA intertwined itself with [Biogen] and appears set to approve the drug regardless. In a year where we've seen other not-ready-for-prime-time approvals (e.g. hydroxychloroquine), we would not be surprised if the agency diverges from the AdCom's recommendations and approves aducanumab.

257. In December 2020, good government advocacy group Public Citizen would publish an open letter calling for an investigation of the FDA's collaboration with Biogen concerning aducanumab, which observed:

> It seems likely that, but for the statistical review provided by Dr. Massie and the intervention of the FDA's [] Advisory Committee — whose members had not been subject to the apparent regulatory capture that compromised the independence and objectivity of the senior staff and clinical reviewers in CDER's Office of Neuroscience — the FDA was prepared to rush to the U.S. market a drug for Alzheimer's disease that lacks substantial evidence of effectiveness, despite these potentially catastrophic impacts.

VIII. PRACTICIONERS, AND EXPERTS BELIEVE THAT ADUCANUMAB SHOULD NOT BE APPROVED

A. Aducanumab Is An Expensive Treatment With No Proven Effect And Whose Effect, Were It To Be Proved, Would Be Clinically Insignificant

258. Biogen estimates that aducanumab would cost about $50,000 per patient per year.[16] Experts estimate that the U.S. may spend more than $20 billion per year on it.

259. To qualify for aducanumab, patients must receive an amyloid PET, a procedure which costs $5,000-$7,000.[17] Moreover, the entire U.S. PET scan capacity is insufficient to aducanumab's needs.[18]

260. Aducanumab is administered through a one-hour infusion every 4 weeks, potentially forever. A caregiver must accompany the patient to the infusion.

261. Aducanumab's side effects include ARIA for APOE4 carriers – about half of all Alzheimer's Disease patients – which is a potentially lethal brain hemorrhage. As Biogen admitted in its Advisory Committee presentation, patients will likely need to undergo routine MRIs to screen for a brain hemorrhage. In aducanumab's Phase III clinical trials, each patient received 7 MRI scans during the 78-week treatment. These scans are time-consuming and expensive. Moreover, there is a risk that unless they are interpreted by specialists like those who worked on the aducanumab Phase III trials, the scans will miss cases of ARIA that could kill patients.

262. The clinical benefit of aducanumab, even if it existed, would be miniscule. As it reported on October 27, 2020, analyst firm UBS had asked five Alzheimer's Disease professionals to report the minimum clinically meaningful reduction. Three of five experts said 1 point on the CDR-SB scale; the two others said 0.5 points. According to an August 2019 article published in Alzheimer's & Dementia, a journal published by the Alzheimer's Association, the minimum

[16] https://www.nytimes.com/2020/11/06/health/aducanumab-alzheimers-drug-fda-panel.html
[17] Comment of the American Academy of Neurology to aducanumab Advisory Committee available for download at https://www.regulations.gov/comment/FDA-2018-N-0410-0029
[18] "There is a clear bottleneck in diagnosis capacity." Defendant Vounatsos, at 2020-01-14 JP Morgan Healthcare Conference.

clinically meaningful improvement is 1 point on the CDR-SB scale. Yet even in EMERGE, the reduction in decline against placebo was 0.4 points on the 18-point CDR-SB scale – below the minimum threshold for a clinically meaningful effect.

263. Dr. David Knopman, a standing Advisory Committee member who was recused from the meeting because he had served as an ENGAGE clinical trial site investigator, submitted a comment urging the Advisory Committee not to recommend approval. Dr. Knopman explained that "the evidence shows [if aducanumab is approved] it will offer improvement to none, it will harm some of those exposed, and it will consume enormous resources."

> I am a behavioral neurologist who has cared for patients with Alzheimer's disease (AD) for nearly 40 years. I care deeply for patients and their families. I desperately wish for a genuine therapy that substantially slows or reverses the disease. Yet the evidence that aducanumab is that therapy and has any benefits in persons with AD is terribly weak. An objective view of the data presented publicly by the sponsor Biogen in December 2019 fails on several key points to prove that aducanumab is efficacious.
> []
> Further, the most optimistic efficacy signal from EMERGE for aducanumab provides no support for a claim of improvement while the magnitude of the slowing of clinical progression is exceedingly small. We acknowledge an inability to extrapolate the effects of aducanumab beyond 18 months, but based on 18 month data, the benefit is of questionable clinical benefit.
> []
> These are extraordinary times for so many reasons, but for the Alzheimer world, a decision by the FDA on November 6 would be transformative - in my view more unfavorable than otherwise. Perfection may be the enemy of the good, but for aducanumab, the evidence doesn't even rise to "good." Contrary to the hope that aducanumab will help Alzheimer patients, the evidence shows it will offer improvement to none, it will harm some of those exposed, and it will consume enormous resources.
>
> The straightforward solution is this: Biogen needs to do a third trial with high dose aducanumab. If the drug's benefits are truly substantial, such a trial could recruit quickly and only several hundred patients would need to be randomized.

264. Approving aducanumab would impose other costs. Aducanumab's approval would at a minimum slow recruitment for clinical trials of other Alzheimer's Disease treatments. Sponsors would have to convince patients to forego aducanumab, an FDA-approved treatment,

in favor of a clinical trial where they would receive either an untried treatment or a placebo. Further, later treatments would have to show they are at least as effective as aducanumab. Aducanumab's results varied both in toto and by subgroup between all of its clinical trials. Even if Biogen's evidence for aducanumab's efficacy were sufficient, the evidence would not show how effective aducanumab is and for which patients. Companies trying to bring effective drugs to market may not be able to show non-inferiority to aducanumab because of the morass of its clinical trial results.

265. The FDA solicited comments concerning aducanumab's approval in connection with the advisory committee meeting. The comments submitted in such circumstances normally heavily favor approval. Incredibly, twice as many comments were opposed to approval as were in favor of it.

B. Biogen Is Cynically Exploiting A Desire By the FDA To Approve A Treatment For Alzheimer's Even If the Treatment Doesn't Work

266. In a November 9, 2020 note, the Director in Chemical Biology & Research in the Novartis Institute for Biomedical Research explained Biogen's rationale in pursuing aducanumab approval:

> [Biogen] have enough of a hint to run a better confirmatory trial, should they so desire, but they do not. They desire to go to the FDA, get the drug approved, and begin printing money.
> And I would be all for a drug company printing money if they had a drug that could really alter the course of Alzheimer's disease, but (once again) Biogen has not, in my opinion, demonstrated that they have anything like that. And I am definitely not all for a drug company printing money for something that really doesn't do anyone any good. Because everyone knows what's going to happen if aducanumab is approved: the pent-up demand for something, anything to treat Alzheimer's is immense. Has been immense forever. There are a lot of people who have a family member with the disease, and they will demand treatment with the new drug that the FDA has approved to fight the disease. Who could blame them?

> []
> And if [the FDA approves aducanumab], we'll find out how many physicians will prescribe it, and how many insurance companies will pay for it. It would be something to see both of these groups hold the line, but I fear that the pressures will be just too great. Biogen is counting on just that, and I'm not happy about it.

267. Extraordinarily, after publication of Dr. Massie's report showed Defendants' statements were false, even investment analysts who covered Biogen opined that approving aducanumab on the basis of the data Biogen presented is not only unlikely, but scientifically and morally wrong:

a. In a November 6, 2020 report, an analyst employed by Raymond James noted:

> Honestly, the panel was a disaster for aducanumab. And it is completely justified. There is no serious scientific argument in favor of anything other than a new prospective study of aducanumab and we can't explain FDA's effusive stance on aducanumab 1) pre-submission, 2) in the briefing documents, and who knows maybe 3) going forward, if they ultimately approve aducanumab.
> If [aducanumab] is approved, 1) futility analyses don't matter, 2) statistics don't matter, 3) AdCom panel votes don't matter, 4) FDA's own guidance/statutes don't matter, and we're left wondering what actually matters in determining what drugs make it to market.[]
> One coherent bull case may be: FDA's credibility is seriously in question already given the irreconcilable interface of the briefing documents and the panel's views, so there is limited credibility left to destroy by approving aducanumab.
>
> **Lastly, FDA should COUNT THE VOTE!**

b. In a November 9, 2020 report, a BMO analyst castigated the FDA on grounds that "[r]ather than seeking ad-com advice as would be customary, it seemed to us that FDA was instead seeking validation for its unorthodox interpretation of a[ducanu]mab clinical data." The analyst called on Biogen to withdraw its BLA outright on moral and scientific grounds, ***regardless of whether it still might be approved***, and start a new Phase III trial.

C. ADDITIONAL FACTS FURTHER PROBATIVE OF SCIENTER

i. "We have nothing to hide"

268. When Biogen presents clinical trial results, it usually provides much more information than it did when it announced aducanumab Phase III results.

269. Defendants themselves acknowledged that the Phase III results they presented were less thorough than usual. For example, in the December 5, 2019 Q&A, an analyst commented that:

> **Q:** I have one for [Sandrock] and one for [Budd Haeberlein], if I may. [Sandrock]***, I've tracked so many of your data presentations over the years. And I felt like today, it seemed like there was so much presented but also so much not presented perhaps. And I couldn't tell why.*** So could you speak to what the carrier and noncarriers look like? And should we assume that vast majority of the patients and the patients that had "sufficient exposure" were noncarriers? That was one for you, [Sandrock].
>
> And [Budd Haeberlein], from your perspective, it seemed like everything we're looking at is a function of 2 things: one is the real data, which is the completers; and one is assumed data, which is the noncompleters. So from your perspective, how – like what was the thought process in getting comfortable assuming that the effect size in noncompleters should mirror the effect size in completers? And is there regulatory feedback and/or sensitivity analyses that support that?
>
> **Defendant Sandrock:** So I guess I'll start with the first question. And Umer, I mean, look, as we said at the very beginning of this call, we're not presenting any data that we didn't already present this morning. ***And you're right, I mean, typically, we do present a lot of things, subgroups included, in the past. You're right, we did do that. There's a time and a place for everything.*** And look, this will soon be under review at regulatory authorities. And so for that reason, we're very sensitive about what we want to present now. ***We have nothing to hide.*** But there's a time and a place for everything. And in due time, I look forward to presenting all the data that make it important for – so that physicians can make the very best benefit/risk decisions if the drug becomes approved.
>
> **Defendant Budd Haeberlein:** Yes. Thanks, Al. I'll just add a comment to that. I'm not sure if I was clear this morning. And that is that the ApoE4 carrier status was well balanced over the arms of each study, was similar in both studies. And this is in the ITT population. But also in that Protocol Version 4 population, ApoE4 carriage was balanced. And that was why we used that particular methodology or one of the reasons. ***So while subgroups are really important***, there's a time and place for us to disclose much more data. I ***think everybody is looking to hear that we have that balance in the studies.***
>
> Umer, to your comment on real data completers versus noncompleters, the analysis method and the data set that we use. So the ITT and the MMRM are in fact the preferred method, as outlined in regulatory guidance on Alzheimer's disease therapeutics. And that was our primary statistical analysis. And so having a prespecified primary statistical analysis plan is what we – one would want to apply when a data set first comes in. However, as we've discussed, given that we had differences between the studies, we went further to do sensitivity analyses, including looking at the completers, to ensure that it wasn't an aspect of early termination that was making the data look the way it was. And as we showed in October, both the ITT and the OTC data sets are equivalent.

270. Indeed, when Biogen presented the Study 103 results, it made the raw data available to researchers.

271. Defendants knew revealing the data would show their explanation for Study 301's failure was false. So they made the out-of-character decision to withhold data with aducanumab's Phase III results.

ii. Defendants Told Investors They Had Taken Exceptional Care In Reviewing and Analyzing the Aducanumab Phase III Clinical Trial Data

272. In response to analyst questions, Defendant Sandrock stated:

> We don't file [for FDA approval] willy-nilly. I mean we only go to filing when we believe that there's a benefit/risk argument based on science, based on data. And look, I mean, if you look at our history, we haven't done filings right and left without good reason. And so – and look, it's a lot of work to do a filing. And it's also a lot of work for FDA or other regulators that have to review a filing. So these are not things that we just do lightly.

PLAINTIFFS' CLASS ACTION ALLEGATIONS

273. Plaintiffs bring this action as a class action pursuant to Federal Rule of Civil Procedure 23(a) and (b)(3) on behalf of a Class, consisting of all those who purchased or otherwise acquired the publicly traded securities of Biogen during the Class Period (the "Class"); and were damaged upon the revelation of the alleged corrective disclosures. Excluded from the Class are Defendants herein, Biogen's officers and directors, at all relevant times, members of their immediate families and their legal representatives, heirs, successors or assigns and any entity in which Defendants have or had a controlling interest.

274. The members of the Class are so numerous that joinder of all members is impracticable. Throughout the Class Period, the Company's securities were actively traded on NASDAQ. While the exact number of Class members is unknown to Plaintiffs at this time and can be ascertained only through appropriate discovery, Plaintiffs believe that there are hundreds or thousands of members in the proposed Class. Record owners and other members of the Class

may be identified from records maintained by Biogen or its transfer agent and may be notified of the pendency of this action by mail, using the form of notice similar to that customarily used in securities class actions.

275. Plaintiffs' claims are typical of the claims of the members of the Class as all members of the Class are similarly affected by Defendants' wrongful conduct in violation of federal law that is complained of herein.

276. Plaintiffs will fairly and adequately protect the interests of the members of the Class and have retained counsel competent and experienced in class and securities litigation. Plaintiffs have no interests antagonistic to or in conflict with those of the Class.

277. Common questions of law and fact exist as to all members of the Class and predominate over any questions solely affecting individual members of the Class. Among the questions of law and fact common to the Class are:

(a) whether Defendants' acts as alleged violated the federal securities laws;

(b) whether Defendants' statements to the investing public during the Class Period misrepresented material facts about the financial condition, business, operations, and management of Biogen;

(c) whether Defendants' statements to the investing public during the Class Period omitted material facts necessary to make the statements made, in light of the circumstances under which they were made, not misleading;

(d) whether the Individual Defendants caused Biogen to issue false and misleading SEC filings and public statements during the Class Period;

(e) whether Defendants acted knowingly or recklessly in issuing false and misleading SEC filings and public statements during the Class Period;

(f) whether the prices of Biogen's securities during the Class Period were artificially inflated because of the Defendants' conduct complained of herein; and

(g) whether the members of the Class have sustained damages and, if so, what is the proper measure of damages.

278. Common questions of law and fact predominate over any questions affecting only individual Class members. Because the common stock of Biogen traded in an efficient market and Defendants' false and misleading statements had impacted the price of Biogen common stock, Plaintiffs will establish reliance for himself and the Class through the fraud-on-the-market doctrine in that:

(a) Defendants made public misrepresentations or failed to disclose material facts during the Class Period;

(b) the omissions and misrepresentations were material;

(c) the Company's securities are traded in an efficient market;

(d) the Company's securities were liquid and traded with moderate to heavy volume during the Class Period;

(e) the Company traded on the NASDAQ, and was covered by many analysts;

(f) the misrepresentations and omissions alleged would tend to induce a reasonable investor to misjudge the value of the Company's securities; Plaintiffs and members of the Class purchased and/or sold the Company's securities between the time the Defendants failed to disclose or misrepresented material facts and the time the true facts were disclosed, without knowledge of the omitted or misrepresented facts; and

(g) Unexpected material news about the Company was rapidly reflected in and incorporated into the Company's stock price during the Class Period.

279. Based upon the foregoing, Plaintiffs and the members of the Class are entitled to a presumption of reliance upon the integrity of the market, establishing predominance.

280. Alternatively, Plaintiffs and the members of the Class are entitled to the presumption of reliance established by the Supreme Court in *Affiliated Ute Citizens of the State of Utah v. United States*, 406 U.S. 128, 92 S. Ct. 2430 (1972), as Defendants omitted material information in their Class Period statements in violation of a duty to disclose such information, as detailed above.

281. A class action is superior to all other available methods for the fair and efficient adjudication of this controversy since joinder of all members is impracticable. Furthermore, as the damages suffered by individual Class members may be relatively small, the expense and burden of individual litigation make it impossible for members of the Class to individually redress the wrongs done to them. There will be no difficulty in the management of this action as a class action.

NO SAFE HARBOR

282. The statutory safe harbor provided for forward-looking statements under certain circumstances does not apply to any of the allegedly false statements pleaded in this Complaint. The statements alleged to be false and misleading herein all relate to then-existing facts and conditions. In addition, to the extent certain of the statements alleged to be false may be characterized as forward looking, they were not identified as "forward-looking statements" when made and there were no meaningful cautionary statements identifying important factors that could cause actual results to differ materially from those in the purportedly forward-looking statements.

COUNT I

Violation of Section 10(b) of The Exchange Act and Rule 10b-5

Against All Defendants

283. Plaintiffs repeat and reallege each and every allegation contained above as if fully set forth herein.

284. Plaintiffs assert this claim against all Defendants, basing the claim upon Section 10(b) of the Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5 promulgated thereunder by the SEC.

285. During the Class Period, in violation of Section 10(b) of the Exchange Act and Rule 10b-5(b), the Company and the Individual Defendants, individually and in concert, directly or indirectly, disseminated or approved the false statements specified above, which they knew or deliberately disregarded were misleading in that they contained misrepresentations, omitted material facts, and failed to disclose material facts necessary to make the statements made, in light of the circumstances under which they were made, not misleading.

286. The Company and the Individual Defendants violated §10(b) of the 1934 Act and Rule 10b-5(a) and (c) in that they employed devices, schemes and artifices to defraud and/or engaged in acts, practices and a course of business that operated as a fraud or deceit upon Plaintiffs and others similarly situated in connection with their purchases of Biogen's securities and directly impacted the price of Biogen's common stock during the Class Period.

287. The Company and the Individual Defendants acted with scienter in that they knew or recklessly disregarded that the public documents and statements issued or disseminated in Biogen's name were materially false and misleading and omitted material information; knew or recklessly disregarded that such statements or documents would be issued or disseminated to the

investing public; and knowingly or recklessly and substantially participated or acquiesced in the issuance or dissemination of such statements or documents as primary violations of the securities laws. These Defendants, by virtue of their receipt of information reflecting the true facts of the Company, their control over, and/or receipt and/or modification of the Company's allegedly materially misleading statements or material omissions, and/or their associations with the Company which made them privy to confidential proprietary information concerning the Company, participated in the fraudulent scheme alleged herein. Information showing that Biogen, by and through the Individual Defendants, and other senior Biogen officers and employees, acted knowingly or with reckless disregard for the truth is peculiarly within Defendants' knowledge and control.

288. The Individual Defendants knew or recklessly disregarded the material omissions and/or the falsity of the material statements set forth above, and intended to deceive Plaintiffs and the other members of the Class, or, in the alternative, acted with reckless disregard for the truth when they failed to ascertain and disclose the true facts in the statements made by them or other Biogen personnel to members of the investing public, including Plaintiffs and the Class.

289. As a direct and proximate result of the scheme or artifice to defraud that lead directly to Biogen's disclosing materially false and misleading information, the market price of Biogen's securities was artificially inflated during the Class Period. In ignorance of the falsity of the statements at issue, Plaintiffs and the other members of the Class relied on the statements described above and/or on the integrity of the market price of Biogen's securities during the Class Period in purchasing the Company's securities at prices that were artificially inflated as a result of Biogen's false and misleading statements and omissions.

290. Had Plaintiffs and the other members of the Class been aware that the market price of Biogen's securities had been artificially and falsely inflated by the fraudulent scheme that caused Biogen to issue misleading financial statements, and by the material adverse information which the Company did not disclose, causing artificial inflation in Biogen's stock price, they would not have purchased Biogen's securities at the artificially inflated prices that they did, or at all.

291. As a result of the wrongful conduct alleged herein, Plaintiffs and other members of the Class have suffered damages in an amount to be established at trial.

292. By reason of the foregoing, Defendants Biogen and the Individual Defendants have violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder and are liable to the Plaintiffs and the other members of the Class for substantial damages which they suffered in connection with their purchases of Biogen's securities during the Class Period.

COUNT II

Violation of Section 20(a) of the Exchange Act

Against the Individual Defendants

293. Plaintiffs repeat and reallege each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

294. During the Class Period, Biogen, by and through its officers and directors, violated Section 10(b) of the Exchange Act and SEC Rule 10b-5 promulgated thereunder.

295. The Individual Defendants participated in the operation and management of Biogen and its operating units, and conducted and participated, directly and indirectly, in the conduct of Biogen's business affairs. As officers and/or directors of a publicly owned company,

the Individual Defendants had a duty to disseminate accurate and truthful information with respect to Biogen's financial condition and results of operations, and to correct promptly any public statements issued by Biogen which had become materially false or misleading.

296. Because of their positions of control and authority as senior officers, the Individual Defendants were able to, and did, control the contents of the various reports, press releases and public filings which Biogen disseminated in the marketplace during the Class Period. Throughout the Class Period, the Individual Defendants exercised their power and authority over Biogen. The Individual Defendants, therefore, were "controlling persons" of Biogen within the meaning of Section 20(a) of the Exchange Act. In this capacity, they participated in the unlawful conduct alleged which artificially inflated the market price of Biogen's securities.

297. Each of the Individual Defendants, therefore, acted as a controlling person of Biogen. By reason of their senior management positions and/or being directors of Biogen, each of the Individual Defendants had the power to direct the actions of, and exercised the same, to cause Biogen to engage in the unlawful acts and conduct complained of herein. Each of the Individual Defendants exercised control over the general operations of Biogen and possessed the power to control the specific activities which comprise the primary violations about which Plaintiffs and the other members of the Class complain.

298. By reason of the foregoing, the Individual Defendants have violated Section 20(a) of the Exchange Act and are jointly and severally liable to the Plaintiffs and the other members of the Class for substantial damages that they suffered in connection with their purchases of Biogen's securities during the Class Period.

PRAYER FOR RELIEF

WHEREFORE, Lead Plaintiff demands judgment against Defendants as follows:

A. Determining that the instant action may be maintained as a class action under Rule 23 of the Federal Rules of Civil Procedure, certifying Plaintiff as Class representative, and approving Lead Counsel and Local Counsel as counsel to the Class;

B. Requiring Defendants to pay damages sustained by Plaintiffs and the Class by reason of the acts and transactions alleged herein;

C. Awarding Plaintiffs and the other members of the Class pre-judgment and post-judgment interest, as well as their reasonable attorneys' fees, expert fees and other costs; and

D. Awarding such other and further relief as this Court may deem just and proper.

DEMAND FOR TRIAL BY JURY

Plaintiff hereby demands a trial by jury.

Dated: April 26, 2021

Respectfully submitted,

THE ROSEN LAW FIRM, P.A.

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